PB82-243999

Hexachlorohexahydromethano-2,4,3-benzodioxathiepin 3-oxide (Endosulfan) Pesticide Registration Standard

(U.S.) Environmental Protection Agency
Washington, DC

Mar 82

U.S. Department of Commerce
National Technical Information Service
NTIS

United States
Environmental Protection
Agency

Office of
Pesticides and Toxic Substances
Washington DC 20460

April 1982

PB82-243999

EPA

Hexachlorohexahydromethano-2,4,3-benzodioxathiepin 3-oxide

(Endosulfan)

Pesticide Registration Standard

REPRODUCED BY
NATIONAL TECHNICAL
INFORMATION SERVICE
U.S. DEPARTMENT OF COMMERCE
SPRINGFIELD, VA. 22161

50272-101

REPORT DOCUMENTATION PAGE

1. REPORT NO. Epa 540/RS-82-008

2.

3. Recipient's Accession No. PB82 243999

4. Title and Subtitle

Pesticide Registration Standard
Endosulfan

5. Report Date MAY 10 1982

6.

7. Author(s) USEPA, Special Pesticide Review Division (SPRD) and Registration Division (RD)

8. Performing Organization Rept. No.

9. Performing Organization Name and Address

U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

10. Project/Task/Work Unit No.

11. Contract(C) or Grant(G) No.
(C)
(G)

12. Sponsoring Organization Name and Address

Same as 9 above.

13. Type of Report & Period Covered

14.

15. Supplementary Notes

16. Abstract (Limit: 200 words)

This document contains information regarding reregistration of pesticide products containing the above chemical including how to register under a registration standard, regulatory position and rationale, and summarizes of data requirements and data gaps. Also included is a bibliography containing citations of all studies reviewed by EPA in arriving at the positions and conclusions contained in the Standard.

17. Document Analysis a. Descriptors

Endosulfan-Pesticide Registration Standard

b. Identifiers/Open-Ended Terms

c. COSATI Field/Group

18. Availability Statement

19. Security Class (This Report) Non-confidential

20. Security Class (This Page)

21. No. of Pages

22. Price

See ANSI-Z39.18)

See Instructions on Reverse

OPTIONAL FORM 272 (4-77)
(Formerly NTIS-35)
Department of Commerce

Endosulfan

Pesticide Registration Standard

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March 1982

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I. HOW TO REGISTER UNDER A REGISTRATION STANDARD

A. Organization of the Standard
B. Purpose of the Standard
C. Requirement to Reregister Under the Standard
D. "Product Specific" Data and "Generic" Data
E. Data Compensation Requirements under FIFRA 3(c)(1)(D)
F. Obtaining Data to Fill "Data Gaps"; FIFRA 3(c)(2)(B)
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A. ORGANIZATION OF THE STANDARD

This first chapter explains the purpose of a registration standard and summarizes the legal principles involved in registering or reregistering under a standard. The second chapter involves the regulatory position and the rationale supporting this position. The third chapter sets forth the data requirements that must be met to obtain or retain registration for products covered by this particular registration standard. In the remaining chapters, the Agency reviews the available data by scientific discipline, discusses the Agency's concerns with the identified potential hazards.

B. PURPOSE OF THE STANDARD

Section 3 of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) provides that "no person in any State may distribute, sell, offer for sale, hold for sale, ship, deliver for shipment, or receive (and having so received) deliver or offer to deliver, to any person any pesticide which is not registered with the Administrator [of EPA]." To approve the registration of a pesticide, the Administrator must find, pursuant to Section 3(c)(5) that:

"(A) its composition is such as to warrant the proposed claims for it;

(B) its labeling and other material required to be submitted comply with the requirements of this Act;

(C) it will perform its intended function without unreasonable adverse effects on the environment; and

(D) when used in accordance with widespread and commonly recognized practice it will not generally cause unreasonable adverse effects on the environment."

In making these findings, the Agency reviews a wide range of data which registrants are required to submit, and assesses the risks and benefits associated with the use of the proposed pesticide. However, the established approach to making these findings has been found to be defective on two counts.

First, EPA and its predecessor agency, the United States Department of Agriculture (USDA), routinely reviewed registration applications on a "product by product" basis, evaluating each product-specific application somewhat independently. In the review of products containing similar components, there was little opportunity for a retrospective review of the full range of pertinent data available in Agency files and in the public literature. Thus the "product by product" approach was often inefficient and sometimes resulted in inconsistent or incomplete regulatory judgments.

Second, over the years, as a result of inevitable and continuing advances in scientific knowledge, methodology, and policy, the data base for many pesticides came to be considered inadequate by current scientific and regulatory standards. Given the long history of pesticide regulation in several agencies, it is even likely that materials may have been lost from the data files. When EPA issued new requirements for registration in 1975 (40 CFR 162) and proposed new guidelines for hazard testing in 1978 (43 FR 29686, July 10, 1978 and 43 FR 37336, August 22, 1978), many products that had already been registered for years were being sold and used without the same assurances of human and environmental safety as was being required for new products. Because of this inconsistency, Congress directed EPA to reregister all previously registered products, so as to bring their registrations and their data bases into compliance with current requirements [See FIFRA Section 3(g)].

Facing the enormous job of re-reviewing and calling-in new data for the approximately 35,000 current registrations, and realizing the inefficiencies of the "product by product" approach, the Agency decided that a new, more effective method of review was needed.

A new review procedure has been developed. Under it, EPA publishes documents called registration standards, each of which discusses a particular pesticide active ingredient. Each registration standard summarizes all the data available to the Agency on a particular active ingredient and its current uses, and sets forth the Agency's comprehensive position on the conditions and requirements for registration of all existing and future products which contain that active ingredient. These conditions and requirements, all of which must be met to obtain or retain full registration or reregistration under Section 3(c)(5) of FIFRA, include the submission of needed scientific data which the Agency does not now have, compliance with standards of toxicity, composition, labeling, and packaging, and satisfaction of the data compensation provisions of FIFRA Section 3(c)(1)(D).

The standard will also serve as a tool for product classification. As part of the registration of a pesticide product, EPA may classify each product for "general use" or "restricted use" [FIFRA Section 3(d)]. A pesticide is classified for "restricted use" when some special regulatory restriction is needed to ensure against unreasonable adverse effects to man or the environment. Many such risks of unreasonable adverse effects can be lessened if expressly-designed label precautions are strictly followed. Thus the special regulatory restriction for a "restricted use" pesticide is usually a requirement that it be applied only by, or under the supervision of, an applicator who has been certified by the State or Federal government as being competent to use the pesticide safely, responsibly, and in accordance with label directions. A restricted-use pesticide can have other regulatory restrictions [40 CFR 162.11(c)(5)] instead of, or in addition to, the certified applicator requirement. These other regulatory restrictions may include such actions as seasonal or regional limitations on use, or a requirement for the monitoring of residue levels after use. A pesticide classified for "general use," or not classified at all, is available for use by any individual who is in compliance with State or local regulations. The registration standard review compares information about potential adverse effects of specific uses of the pesticide with risk criteria listed in 40 CFR 162.11(c), and thereby determines whether a product needs to be classified for "restricted use." If the standard does classify a pesticide for "restricted use," this determination is stated in the second chapter.

C. REQUIREMENT TO REREGISTER UNDER THE STANDARD

FIFRA Section 3(g), as amended in 1978, directs EPA to reregister all currently registered products as expeditiously as possible. Congress also agreed that reregistration should be accomplished by the use of registration standards.

Each registrant of a currently registered product to which this standard applies, and who wishes to continue to sell or distribute his product in commerce, must apply for reregistration. His application must contain proposed labeling that complies with this standard.

EPA will issue a notice of intent to cancel the registration of any currently registered product to which this standard applies if the registrant fails to comply with the procedures for reregistration set forth in the Guidance Package which accompanies this standard.

D. "PRODUCT SPECIFIC" DATA AND "GENERIC" DATA

In the course of developing this standard, EPA has determined the types of data needed for evaluation of the properties and effects of products to which the standard applies, in the disciplinary areas of Product Chemistry, Environmental Fate, Toxicology, Residue Chemistry, and Ecological Effects. These determinations are based primarily on the data Guidelines proposed in 43 FR 29696, July 10, 1978; 43 FR 37336, August 22, 1978; and 45 FR 72948, November 3, 1980, as applied to the use patterns of the products to which this standard applies. Where it appeared that data from a normally applicable Guidelines requirement was actually unnecessary to evaluate these products, the standard indicates that the requirement has been waived. On the other hand, in some cases studies not required by the Guidelines may be needed because of the particular composition or use pattern of products the standard covers; if so, the standard explains the Agency's reasoning. Data guidelines have not yet been proposed for the Residue Chemistry discipline, but the requirements for such data have been in effect for some time and are, the Agency believes, relatively familiar to registrants. Data which we have found are needed to evaluate the registrability of some products covered by the standard may not be needed for the evaluation of other products, depending upon the composition, formulation type, and intended uses of the product in question. The standard states which data requirements apply to which product categories. (See the third chapter.) The various kinds of data normally required for registration of a pesticide product can be divided into two basic groups:

1. Data that are product specific, i.e. data that relate only to the properties or effects of a product with a particular composition (or a group of products with closely similar composition); and

2. Generic data that pertains to the properties or effects of a particular ingredient, and thus are relevant to an evaluation of the risks and benefits of all products containing that ingredient (or all such products having a certain use pattern), regardless of any such product's unique composition.

The Agency requires certain "product specific" data for each product to characterize the product's particular composition and physical/chemical properties (Product Chemistry), and to characterize the product's acute toxicity (which is a function of its total composition). The applicant for registration or reregistration of any product, whether it is a manufacturing-use or end-use product, and without regard to its intended use pattern, must submit or cite enough of this kind of data to allow EPA to evaluate the product. For such purposes, "product specific" data on any product other than the applicant's is irrelevant, unless the other product is closely similar in composition to the applicant's. (Where it has been found practicable to group similar products for purposes of evaluating, with a single set of tests, all products in the group, the standard so indicates.) "Product specific" data on the efficacy of particular end-use products are also required where the exact formulation may affect efficacy and where failure of efficacy could cause public health problems.

All other data needed to evaluate pesticide products concern the properties or effects of a particular ingredient of products (normally a pesticidally active ingredient, but in some cases a pesticidally inactive, or "inert", ingredient). Some data in this "generic" category are required to evaluate the properties and effects of all products containing that ingredient [e.g., the acute LD-50 of the active ingredient in its technical or purer grade; see proposed guidelines, 43 FR 37355].

Other "generic" data are required to evaluate all products which both contain a particular ingredient and are intended for certain uses (see, e.g., proposed guidelines,43 FR 37363, which requires subchronic oral testing of the active ingredient with respect to certain use patterns only). Where a particular data requirement is use-pattern dependent, it will apply to each end-use product which is to be labeled for that use pattern (except where such end-use product is formulated from a registered manufacturing-use product permitting such formulations) and to each manufacturing-use product with labeling that allows it to be used to make end-use products with that use pattern. Thus, for example, a subchronic oral dosing study is needed to evaluate the safety of any manufacturing-use product that legally could be used to make an end-use, food-crop pesticide. But if an end-use product's label specified it was for use only in ways that involved no food/feed exposure and no repeated human exposure, the subchronic oral dosing study would not be required to evaluate the product's safety; and if a manufacturing-use product's label states that the product is for use only in making end-use products not involving food/feed use or repeated human exposure, that subchronic oral study would not be relevant to the evaluation of the manufacturing-use product either.

If a registrant of a currently registered manufacturing-use or end-use product wishes to avoid the costs of data compensation [under FIFRA Section 3(c)(1)(D)] or data generation [under Section 3(c)(2)(B)] for "generic" data that is required only with respect to some use patterns, he may elect to delete those use patterns from his labeling at the time he reregisters his product. An applicant for registration of a new product under this standard may similarly request approval for only certain use patterns.

E. DATA COMPENSATION REQUIREMENTS UNDER FIFRA 3(c)(1)(D)

Under FIFRA Section 3(c)(1)(D), an applicant for registration, reregistration, or amended registration must offer to pay compensation for certain existing data the Agency has used in developing the registration standard. The data for which compensation must be offered are all data which are described by all of the following criteria:

1. The data were first submitted to EPA (or to its predecessor agencies, USDA or FDA), on or after January 1, 1970;
2. The data were submitted to EPA (or USDA or FDA) by some other applicant or registrant in support of an application for an experimental use permit, an amendment adding a new use to a registration, or for registration, or to support or maintain an existing registration;
3. They are the kind of data which are relevant to the Agency's decision to register or reregister the applicant's product under the Registration Standard, taking into account the applicant's product's composition and intended use pattern(s);
4. The Agency has found the data to be valid and usable in reaching regulatory conclusions; and
5. They are not data for which the applicant has been exempted by FIFRA Section 3(c)(2)(D) from the duty to offer to pay compensation. (This exemption applies to the "generic" data concerning the safety of an active ingredient of the applicant's product, not to "product specific" data. The exemption is available only to applicants whose product is labeled for end-uses for which the active ingredient in question is present in the applicant's product because of his use of another registered product containing that active ingredient which he purchases from another producer.

An applicant for reregistration of an already registered product under this standard, or for registration of a new product under this standard, accordingly must determine which of the data used by EPA in developing the standard must be the subject of an offer to pay compensation, and must submit with his application the appropriate statements evidencing his compliance with FIFRA Section 3(c)(1)(D).

An applicant would never be required to offer to pay for "product specific" data submitted by another firm. In many, if not in most cases, data which are specific to another firm's product will not suffice to allow EPA to evaluate the applicant's product, that is, will not be useful to the Agency in determining whether the applicant's product is registrable. There may be cases, however, where because of close similarities between the composition of two or more products, another firm's data may suffice to allow EPA to evaluate some or all of the "product specific" aspects of the applicant's product. In such a case, the applicant may choose to cite that data instead of submitting data from tests on his own product, and if he chooses that option, he would have to comply with the offer-to-pay requirements of Section 3(C)(1)(D) for that data.

Each applicant for registration or reregistration of a manufacturing-use product, and each applicant for registration or reregistration of an end-use product, who is not exempted by FIFRA Section 3(c)(2)(D), must comply with the Section 3(c)(1)(D) requirements with respect to each item of "generic" data that relates to his product's intended uses.

A detailed description of the procedures an applicant must follow in applying for reregistration (or new registration) under this standard is found in the Guidance Package for this standard.

F. OBTAINING DATA TO FILL "DATA GAPS"; FIFRA 3(c)(2)(B)

Some of the kinds of data EPA needs for its evaluation of the properties and effects of products to which this standard applies have never been submitted to the Agency (or, if submitted, have been found to have deficiencies rendering them inadequate for making registrability decisions) and have not been located in the published literature search that EPA conducted as part of preparing this standard. Such instances of missing but required data are referred to in the standard as "data gaps".

FIFRA Section 3(c)(2)(B), added to FIFRA by the Congress in 1978, authorizes EPA to require registrants to whom a data requirement applies to generate (or otherwise produce) data to fill such "gaps" and submit those data to EPA. EPA must allow a reasonably sufficient period for this to be accomplished. If a registrant fails to take appropriate and timely steps to fill the data gaps identified by a section 3(c)(2)(B) order, his product's registration may be suspended until the data are submitted. A mechanism is provided whereby two or more registrants may agree to share in the costs of producing data for which they are both responsible.

The standard lists, in the third chapter, the "generic" data gaps and notes the classes of products to which these data gaps pertain. The standard also points out that to be registrable under the standard, a product must be supported by certain required "product specific" data. In some cases, the Agency may possess sufficient "product specific" data on one currently registered product, but may lack such data on another. Only those standards which apply to a very small number of currently registered products will attempt to state definitively the "product specific" data gaps on a "product by product" basis. (Although the standard will in some cases note which data that EPA does possess would suffice to satisfy certain "product specific" data requirements for a category of products with closely similar composition characteristics.)

As part of the process of reregistering currently registered products, EPA will issue Section 3(c)(2)(B) directives requiring the registrants to take appropriate steps to fill all identified data gaps — whether the data in question are "product specific" or "generic" — in accordance with a schedule.

Persons who wish to obtain registrations for new products under this standard will be required to submit (or cite) sufficient "product specific" data before their applications are approved. Upon registration, they will be required under Section 3(c)(2)(B) to take appropriate steps to submit data needed to fill "generic" data gaps. (We expect they will respond to this requirement by entering into cost-sharing agreements with other registrants who previously have been told they must furnish the data.) The Guidance Package for this standard details the steps that must be taken by registrants to comply with Section 3(c)(2)(B).

G. Amendments to the Standard

Applications for registration which propose uses or formulations that are not presently covered by the standard, or which present product compositions, product chemistry data, hazard data, toxicity levels, or labeling that do not meet the requirements of the standard, will automatically be considered by the Agency to be requests for amendments to the standard. In response to such applications, the Agency may request additional data to support the proposed amendment to the Standard, or may deny the application for registration on the grounds that the proposed product would cause unreasonable adverse effects to the environment. In the former case, when additional data have been satisfactorily supplied, and providing that the data do not indicate the potential for unreasonable adverse effects, the Agency will then amend the Standard to cover the new registration.

Each registration standard is based upon all data and information available to the Agency's reviewers on a particular date prior to the publication date. This "cut-off" date is stated at the beginning of the second chapter. Any subsequent data submissions and any approved amendments will be incorporated into the Registration Standard by means of addenda, which are available for inspection at EPA in Washington, D.C., or copies of which may be requested from the Agency. When all the present "data gaps" have been filled and the submitted data have been reviewed, the Agency will revise the Registration Standard. Thereafter, when the Agency determines that the internally maintained addenda have significantly altered the conditions for registration under the standard, the document will be updated and re-issued.

While the registration standard discusses only the uses and hazards of products containing the designated active ingredient(s), the Agency is also concerned with the potential hazards of some inert ingredients and impurities. Independent of the development of any one standard, the Agency has initiated the evaluation of some inert pesticide ingredients. Where the Agency has identified inert ingredients of concern in a specific product to which the standard applies, these ingredients will be pointed out in the Guidance Package.

II. REGULATORY POSITION AND RATIONALE

A. Introduction
B. Description of Chemical
C. Regulatory Position
D. Regulatory Rationale
E. Criteria for Registration Under the Standard
F. Acceptable Ranges and Limits
G. Required Labeling
H. Tolerance Reassessment
I. New and Amended Registrations Under this Standard

A. INTRODUCTION

This chapter presents the Agency's regulatory position and rationale based on an evaluation of all registered products containing endosulfan as the sole active ingredient. The regulatory position contained in the standard reflects a review of this chemical and not of other active ingredients in a mixture. After briefly describing endosulfan, this chapter presents the regulatory position and rationale, and the criteria for registration of products containing this chemical. Also included in this chapter are labeling considerations and the tolerance reassessment. A summary of data requirements is contained in Chapter III. Data supporting this regulatory position are discussed in each of the disciplinary chapters, IV through VIII.

B. DESCRIPTION OF CHEMICAL

Endosulfan is the common name for hexachlorohexahydromethano-2,4,3-benzodioxathiepin 3-oxide. It is registered with the U.S. Environmental Protection Agency as a broad spectrum insecticide/acaricide.

Endosulfan formulated products are marketed under various trades names such as Beosit, Chlorthiepin, Cyclodan, Insectophene, Kop-Thiodan, Malix, Thifor, Thimul, Thiodan, Thionex, and Tiovel. These products represent a wide range of end-use formulations including dusts, wettable powders, granulars, emulsifiable concentrates, pressurized liquids, and impregnated materials.

C. REGULATORY POSITION

The Agency has reviewed the scientific data obtained from the open literature as of September 30, 1981, and the data submitted by the registrants up through the time of the publication of this standard. Based on this review, the Agency has made the following determinations:

- Pesticide products containing endosulfan as the sole active ingredient may be registered, subject to the terms and conditions specified in this standard.

- The risk criteria for hazardous effects on aquatic species may be exceeded for the use of this active ingredient on watercress (40 CFR 162.11(a)(3)(i)(B)(3) and 40 CFR 162.11(a)(3)(ii)(B); however, more information is required for this determination.

- The use on alfalfa, blueberries, citrus (all), corn, cotton, lettuce, logs (felled), pecans, pineapples, soybeans, sugarcane, sunflower, tobacco, and tomatoes may also exceed the criterion for risk to endangered species (40 CFR 162.11(a)(3)(ii)(B).

- The registrant must develop or agree to develop additional data, specified in Chapter III, to maintain the existing registration or to obtain new registrations.

- The tolerances for the registered uses on agricultural crops are supported by the residue data submitted, except where noted in Chapter III.

D. REGULATORY RATIONALE

A review of the available data regarding the manufacturing-use and end-use products of endosulfan shows that much of the information on toxicology and environmental fate is invalid and not useful for registration. Although these data requirements are still outstanding, the Agency has concluded that it should continue the registration for this chemical for the following reasons.

The Pesticide Incidence Monitoring System (PIMS) found 91 reports of human poisoning and ecological effects incidents related to the use of endosulfan. Only one third were reports of endosulfan as the sole active ingredient. Some of the reports concerned accidental poisonings due to improper methods of application, or accidents during the manufacture of the material. Many of the reports were unsubstantiated. No regulatory changes based on these data will be required.

The Agency has concluded that information is insufficient to determine whether the direct application to water during the treatment of watercress poses the risk of unreasonable effects on the aquatic environment. Submitted studies demonstrate that endosulfan has a high level of toxicitiy to a wide variety of aquatic species and use on watercress will theoretically result in residues at the application site exceeding the LC_{50} values for all aquatic species tested. However, before determining whether a Rebuttable Presumption Against Registration (RPAR) has arisen with respect to risk to aquatic organisms, the Agency must consider the actual or potential exposure of non-target aquatic organisms to the residues resulting from the application of endosulfan to watercress. To determine these exposure levels, the Agency must have additional monitoring information from which it can assess the potential for contamination of freshwater and estuarine environments by various pathways.

Should the required monitoring information demonstrate actual or potential exposure to aquatic non-target or endangered species, the Agency will attempt to resolve any factual issues through consultation with the registrants before issuing a Notice of Rebuttable Presumption Against Registration (RPAR) for the use of endosulfan on watercress.

Regarding the protection of all aquatic species, monitoring data will be required on the levels of endosulfan in the aquatic environment resulting from terrestrial applications.

Regarding the protection of endangered species from the use of endosulfan, the Agency prepared a request for a formal consultation with the Office of Endangered Species, U.S. Fish and Wildlife Service, U.S. Department of the Interior on February 4, 1982 (as required by Section 7 of the Endangered Species Act of 1973, as amended). The sites of concern are alfalfa, blueberries, citrus (all), corn, cotton, lettuce, logs (felled), pecans, pineapples, soybeans, sugarcane, sunflower, tobacco, tomatoes, and watercress.

In accordance with FIFRA, the Agency's policy is not to cancel or to withhold registration merely for the lack of data. (See sections 3(c)(2)(B) and 3(c)(7) of FIFRA). Rather, publication of the standard provides a mechanism for identifying data needs, and registration under the standard allows for upgrading of labels during the period in which the required data are being generated. When these data are received, they will be reviewed by the Agency. The Agency will then determine whether these data will warrant further regulatory action.

E. CRITERIA FOR REGISTRATION UNDER THE STANDARD

To be subject to this standard, products must meet the following conditions:

- contain endosulfan as the sole active ingredient; and
- bear required labeling; and
- conform to the acute toxicity limits, product composition and use pattern requirements stated in Section F, below.

An applicant for registration or reregistration of products subject to this standard must comply with all terms and conditions described in this standard including a commitment to fill data gaps on a time schedule specified by the Agency and, when applicable, offering to pay compensation to the extent required by 3(c)(1)(D) of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), as amended, 7 U.S.C. 136a(c)(1)(D).

F. ACCEPTABLE RANGES AND LIMITS

1. Manufacturing-Use Products

a. Product Composition Standard

To be eligible for registration/reregistration under this standard, technical grade products must contain endosulfan as their sole active ingredient and such products may contain endosulfan in the range of 94-96 percent active ingredient. In addition, these products must not contain impurities other than those in currently registered technical grade products and at no higher concentration than those in currently registered products. Any technical product not meeting these requirements will be considered to be a new product and will not be registerable under this standard.

For a manufacturing-use product other than a technical, a registered technical must be used and it must be used to produce an acceptable end-use product. Any manufacturing-use product not meeting these requirements will be considered to be a new product and will not be registerable under this standard.

Manufacturing-use products meeting these requirements may contain any percentage active ingredientup to 96 percent.

b. Acute Toxicity Limits

The Agency will consider registration of manufacturing-use products containing endosulfan regardless of the toxicity category, provided that the labeling of such products bears appropriate precautionary statements.

c. Use Patterns and Application

To be registered under this standard, manufacturing-use products containing endosulfan must be labeled to allow for formulation of insecticide/acaracide products approved by the Agency in one or more of the following use categories:

-Domestic outdoor use
-Greenhouse use
-Tree fruit and nut crops
-Field and vegetable crops
-Aquatic food use (watercress)
-Forestry use

2. End-Use Products

a. Product Composition Standard

End-use formulations may contain up to the following percent active ingredient: dust - 5 percent; granular - 3 percent; wettable powder - 50 percent; emulsifiable concentrate - 34 percent; pressurized liquid - 10 percent; and impregnated material - 15 percent. For formulations intended for food-use, all the inerts must be cleared under 40 CFR 180.1001. The appropriate certification of limits must be provided and the application rates per acre basis must remain the same or less.

b. Acute Toxicity Limits

The Agency will consider for registration end-use products in Toxicity Category II, III, and IV. This consideration, is predicated upon label incorporations of appropriate hazard warnings, as well as precautionary and use restrictions as required. There are no currently registered end-use products in Toxicity Category I. Any products submitted for registration in this category would require supporting data, and would not be registerable under this standard.

c. Use Patterns

To be considered under this standard, end-use products must bear directions for uses as an insecticide/acaracide, which are intended for ground and/or aerial applications to one or more of the following use categories:

- -Domestic outdoor use
- -Greenhouse use
- -Tree fruit and nut crops
- -Field and vegetable crops
- -Aquatic food use (watercress)
- -Forestry use

G. REQUIRED LABELING

All manufacturing-use and end-use endosulfan products must bear appropriate labeling as specified in 40 CFR 162.10. The guidance package which accompanies this standard contains specific information regarding labeling requirements.

1. Manufacturing-Use Products

a. Use Pattern Statements

All manufacturing-use products containing endosulfan must list on the label a statement which provides that the product may be used only in the formulation of insecticide/acaracide products approved by the Agency for one or more of the following use categories:

- -Domestic outdoor use
- -Greenhouse use
- -Tree fruit and nut crops
- -Field and vegetable crops
- -Aquatic food use (watercress)
- -Forestry use

b. Precautionary Statements

Because of the absence of data needed to assess the environmental and health hazards of endosulfan, the Agency cannot evaluate the adequacy of precautionary statements on manufacturing-use product labels. Therefore, no changes to current label statements are required at this time. The Agency may, after review of all data to be submitted under this standard, require revisions to current labels and may also impose additional label requirements.

2. End-Use Products

a. Use Pattern Statements

Additional labeling restrictions may be required to protect endangered species. The possible necessity for this labeling can be determined only after completion of the formal consultation with the Office of Endangered Species.

b. Precautionary Statements

Because of the absence of data needed to assess the environmental and health hazards of endosulfan, the Agency cannot evaluate the adequacy of precautionary statements on end-use product labels. Therefore, no changes to current label statements are required at this time. The Agency may, after review of all data to be submitted under this standard, require revisions to current labels and may also impose additional label requirements.

H. TOLERANCE REASSESSMENT

A listing of the tolerances for residues of endosulfan in or on raw agricultural commodities in the United States as stated in 40 CFR 180.182 is found in Chapter VII. A list of the CODEX tolerances is also found in Chapter VII.

The toxicology tests on endosulfan demonstrate that the chemical may induce adverse effects, especially liver and kidney effects, and testicular atrophy. However, the no observable effect level (NOEL) has not yet been established, nor has the reversibility of these effects been demonstrated adequately. Sufficient information does exist to utilize 30 ppm as a provisional NOEL, and because sufficient data exist to suggest the the NOEL, once firmly established, will not be significantly below the 30 ppm level, a 100X safety factor can be utilized.

A 30 ppm NOEL equates to a 0.75 mg/kg/day NOEL for humans, yielding an acceptable daily intake (ADI) of 0.0075 mg/kg/day (the maximum permissable intake or MPI is 0.45 mg/day for a 60 kg person). The existing food tolerances yield a theoretical maximum residue contribution (TMRC) of 0.6314 mgper day, which is 140 percent of the MPI as calculated from the provisional NOEL. Therefore, it is necessary to require the data to establish the NOEL and also, to re-examine existing tolerance levels to determine if they are truly representative of the actually occuring residues on foods.

A final reassessment of all endosulfan tolerances cannot be made at this time since there are several registration/tolerance data requirements which have not been satisfied. Until these gaps are filled, the Agency is unable to estimate the contribution of the by-products apple pomace, grape pomace, tomatoe pomace, and pineapple bran to residues in meat and milk.

III. SUMMARY OF DATA REQUIREMENTS AND DATA GAPS

Applicants for registration of manufacturing-use and end-use endosulfan products must cite or submit the information identified in the tables in this chapter. The tables applicable to end-use products indicate whether the product to be tested is the technical grade or formulation. Data generated on one formulation may be used to satisfy the data requirement for a substantially similar formulation. Information on which product specific data requirements are already met is available in the guidance package.

Before each requirement is listed the section of the Proposed Guidelines which describes the type of data and when the data are required to be submitted (43 FR, 29696 of July 10, 1978; 43 FR, 37336 of August 22, 1978; and 45 FR, 72948 of November, 3, 1980). Justification for the test requirement is provided in the Guidelines. A discussion of why data additional to those already submitted are necessary, or why data normally required are not necessary for this chemical, are explained in footnotes to the tables. The data requirements specified are the minimum that will be required. Areas where additional data may be required as the result of tiered testing are indicated.

DATA REQUIREMENTS CHART A

ENDOSULFAN

Generic Data Requirements: ENVIRONMENTAL FATE

Guidelines Citation	Name of Test	When Required[1]	Composition	Does EPA have data to partially or totally satisfy this requirement?	Bibliographic Citation	Must additional da be submitted under FIFRA 3(c)(2)(B)? If so, due when?
163.62-7(b)	Hydrolysis	A,B,C,D,E,F	2/	Partially	05012725, 05003007 05005315	Yes/8 months[3]
163.62-7(c)	Photodegradation	C,D,E,F	2/	Partially	05002841	Yes/8 months[4]
163.62-8(b)	Aerobic Soil Metabolism	A,B,C,D,F	2/	Partially	05005047	Yes/26 months[5]
163.62-8(c)	Anaerobic Soil Metabolism	D	2/	Partially	05005047	Yes/26 months[5]
163.62-8(d)	Anaerobic Aquatic Metabolism	E,F	2/	No		Yes/26 months[6]
163.62-8(e)	Aerobic Aquatic Metabolism	E	2/	No		Yes/26 months
163.62-8(f)	Microbiological				05003471, 05005315 05003007, 05012725 05013674, 05017001 05004262, 05004617 05010061	Reserved[7]
163-62-8(g)	Activated Sludge				-	Reserved[7]
163.62-9(b)	Leaching	C,D	2/	No	-	Yes/14 months
163.62-9(c)	Volatility	B	Technical Grade of Active Ingredient	Partially	05013707, 05019845 05002841	Yes/14 months[8]
163.62-9(d)	Adsorption/Desorption	A,B,C,D,E,F	2/	No	-	Yes/14 months

These data requirements are based on the draft registration guidelines published on July 10, 1978 (43 FR 29696). These testing requirements are based on proposed guidelines. Registrants are advised to consult with the Agency prior to initiating these tests.

1/ This column specifies the use sites for which the data are required using the following codes: A= Domestic outdoor; B= Greenhouse; C= Tree fruit and nut crop; D= Field and vegetable crop; E= Aquatic food use (watercress); F= Forestry use.
2/ Radiolabeled analytical grade or nonradiolabeled technical grade material.
3/ These studies were done primarily to study the microbial degradation of endosulfan. The hydrolysis properties were not fully detailed.
4/ The analysis for photolysis products was only conducted once. Therefore, no conclusion can be drawn on the rate of endosulfan degradation.
5/ Data are insufficient to determine the rate of metabolism in soil. Data are needed using sampling intervals that are adequate to determine the half-life of endosulfan and the rate of formation and decline of the endosulfan metabolites.
6/ This study may substitute for the anaerobic soil metabolism study (163.62-8(c)), but the reverse is not true.
7/ The requirement for the submission of these data is reserved, pending the review and modification of the testing protocols.
8/ Full analytical procedural details were missing, but the studies did provide information for estimating expected background levels of endosulfan in agricultural areas.

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ENVIRONMENTAL FATE CONTINUED

Guidelines Citation	Name of Test	When Required 1/	Composition	Does EPA have data to partially or totally satisfy this requirement?	Bibliographic Citation	Must additional data be submitted under FIFRA 3(c)(2)(B)? If so, due when?
163.62-9(e)	Water Dispersal	E	A Representive Formulation	No	-	Yes/14 months
163.62-10(b)	Terrestrial Field Dissipation	A,C,D,E,F	A Representative Formulation	Partially	00003800, 05003336	Yes/14 months 2/
163.62-10(c)	Aquatic Field Disspiation	E,F	A Representative Formulation	No	-	Yes/14 months
163.62-10(d)	Dissipation-Forestry	F	A Representative Formulation	No	-	Yes/14 months
163.62-10(e)	Aquatic Impact Uses	E	A Representative Formulation	No	-	Yes/14 months
163.62-10(g)	Long Term Field Dissipation	A,C,D,E,F			-	Reserved 3/
163.62-11(c)	Accumulation in Irrigated Crops	E	4/	No	-	Yes/14 months
163.62-11(d)	Fish Accumulation	C,D,E,F	5/	Yes	05005824, 05003053	No
163.62-13	Disposal & Storage					Reserved 6/

These data requirements are based on the draft registration guidelines published on July 10, 1978 (43 FR 29696). These testing requirements are based on proposed guidelines. Registrants are advised to consult with the Agency prior to initiating these tests.

1/ This column specifies the use sites for which the data are required using the following codes: A= Domestic outdoor; B= Greenhouse; C= Tree fruit and nut crop; D= Field and vegetable crop; E= Aquatic food use (watercress); F= Forestry use.

2/ Additional studies are needed to fulfill the requirements in this section in order to determine the terrestrial dissipation rate. The Agency will need to see the proposed protocols for and results of specific runoff monitoring studies. Formulations to be tested must be specified and the ecological appropriateness of the study plots must be assessed by the Agency prior to approval of the protocols.

3/ The requirement for this test depends on results of 163.62-8(b), 163.62-11, 163.62-10(b)(1), and 163.62-11(d).

4/ Radiolabeled analytical grade, if residues are found, then a field test using a representative formulation product.

5/ Radiolabeled analytical grade or nonradiolabeled technical grade material.

6/ The requirement for the submission of these data is reserved, pending the review and modification of testing protocols.

DATA REQUIREMENTS CHART A

ENDOSULFAN

Generic Data Requirements: TOXICOLOGY

Guidelines Citation	Name of Test	When Required[1]	Composition	Does EPA have data to partially or totally satisfy this requirement?	Bibliographic Citation	Must additional data be submitted under FIFRA 3(c)(2)(B)? If so, due when?
163.81-1	Acute Oral Toxicity	A,B,C,D,E,F	Technical Grade of Active Ingredient	Yes	00003762, 00003693 GS014007, 05002183 GS014001, 05003703	No
163.81-2	Acute Dermal Toxicity	A,B,C,D,E,F	Technical Grade of Active Ingredient	Yes	05003718	No
163.81-3	Acute Inhalation Toxicity	A,B,C,D,E,F	Technical Grade of Active Ingredient	Yes	05007645, GS014005	No
163.81-4	Primary Eye Irritation	A,B,C,D,E,F	Technical Grade of Active Ingredient	Yes	GS014004	No
163.81-5	Primary Dermal Irritation	A,B,C,D,E,F	Technical Grade of Active Ingredient	Yes	GS014003	No
163.81-6	Dermal Sensitization	A,B,C,D,E,F	Technical Grade of Active Ingredient	No	-	Yes/8 months
163.81-7	Acute Delayed Neurotoxicity	A,B,C,D,E,F	Technical Grade of Active Ingredient	Partially	05011227, 05007646 05004972	Yes/14 months[2]
163.82-1	Subchronic Oral Toxicity	A,B,C,D,E,F	Technical Grade of Active Ingredient	No	-	Yes/14 months
163.82-2	21-Day Subchronic Dermal Toxicity	A,B,C,D,E,F	Technical Grade of Active Ingredient	No	-	Yes/14 months

These tables reflect the toxicological questions we have about endosulfan and, by reference to the guidelines, possible ways these questions may be answered. The guidelines represent one way these questions may be answered but certainly not the only way. This pesticide is unusual in that there is a mass of toxicological data available. While many of the individual toxicological studies considered in this standard are not adequate to fill specific data gaps, in there entirety these studies do contain some toxicological information. Some of the remaining toxicology questions may be resolved by more simple thus less expensive toxicology studies if used in conjunction with the toxicology data discussed in this document.

[1] This column specifies the use sites for which the data are required using the following codes: A= Domestic outdoor; B= Greenhouse; C= Tree fruit and nut crop; D= Field and vegetable crop; E= Aquatic food use (watercress); F= Forestry use.

[2] Endosulfan does not relate to a known group of cholinesterase inhibitors, but there are indications of cholinesterase inhibition. Further testing is therefore required. The neurological effects may be included as an additional parameter in the subacute and/or chronic studies.

TOXICOLOGY CONTINUED

Guidelines Citation	Name of Test	When Required[1/]	Composition	Does EPA have data to partially or totally satisfy this requirement?	Bibliographic Citation	Must additional data be submitted under FIFRA 3(c)(2)(B)? If so, due when?
163.82-4	Subchronic Inhalation Toxicity	A,B,C,D,E,F	Technical Grade of Active Ingredient	No	-	Yes/14 months
163.82-5	Subchronic Neuro-toxicity	-	-	-	-	Reserved[2/]
163.83-1	Chronic Feeding	C,D,E	Technical Grade of Active Ingredient	Partially	00003604, 00003741 00003602	Yes/50 months[3/]
163.83-2	Oncogenicity	C,D,E	Technical Grade of Active Ingredient	Partially	00004256, 05010016	Yes/50 months[4/]
163.83-3	Teratogenicity	A,C,D,E	Technical Grade of Active Ingredient	Yes	GS014008, GS014023	No
163.83-4	Reproduction	A,C,D,E	Technical Grade of Active Ingredient	No	-	Yes/38 months
163.84-2 through -4	Mutagenicity	A,C,D,E	Technical Grade of Active Ingredient	Partially	00003711, GS014009	Yes/26 months[5/]

These tables reflect the toxicological questions we have about endosulfan and, by reference to the guidelines, possible ways these questions may be answered. The guidelines represent one way these questions may be answered but certainly not the only way. This pesticide is unusual in that there is a mass of toxicological data available. While many of the individual toxicological studies considered in this standard are not adequate to fill specific data gaps, in there entirety these studies do contain some toxicological information. Some of the remaining toxicology questions may be resolved by more simple thus less expensive toxicology studies if used in conjunction with the toxicology data discussed in this document.

1/ This column specifies the use sites for which the data are required using the following codes: A= Domestic outdoors; B= Greenhouse;
C= Tree fruit and nut crop; D= Field and vegetable crop; E= Aquatic food use (watercress); F= Forestry use.
2/ The decision of whether testing is required cannot be made until the results of the acute delayed neurotoxicity testing are submitted and reviewed.
3/ Because of the inadequacies in the submitted rat study, an additional study will need to be conducted on the rat.
4/ The studies submitted were inconclusive due to improper testing protocols. Further oncogenic testing is required using both the rat and mouse.
5/ The Agency requires a battery of valid mutagenicity tests which demonstrate the potency of the chemical to induce point and chromosomal mutations, either directly or indirectly. After the results of the testing have been considered, additional testing may be required to further characterize or quantify the potential genetic risks. Although the Agency's mutagenic testing requirements are not final, the standards for these tests should be based on the principles set forth in 43 FR 37388. Protocols and choices of test systems should be accompanied by a scientific rationale. Substitutions of test systems will be considered after discussion with the Agency. As the submitted studies indicated a negative dominant lethal response and no mutagenic potential in bacteria, the Agency will consider these requirements fulfilled.

Guidelines Citation	Name of Test	When Required[1/]	Composition	Does EPA have data to partially or totally satisfy this requirement?	Bibliographic Citation	Must additional data be submitted under FIFRA 3(c)(2)(B)? If so, due when?
163.85-1	Metabolism (Identification of Metabolites)	C,D,E	Radiolabeled Analytically Pure Grade of Active Ingredient	Yes	05003703, 00004257 00003761, 05007464 05003503	No
163.86-1	Domestic Animal Safety	A,B,C,D,E,F	-	Yes	00003603	No
	Special Studies:					
	Emergency Treatment	A,B,C,D,E,F	-	No	-	Yes/14 months

These tables reflect the toxicological questions we have about endosulfan and, by reference to the guidelines, possible ways these questions may be answered. The guidelines represent one way these questions may be answered but certainly not the only way. This pesticide is unusual in that there is a mass of toxicological data available. While many of the individual toxicological studies considered in this standard are not adequate to fill specific data gaps, in there entirety these studies do contain some toxicological information. Some of the remaining toxicology questions may be resolved by more simple thus less expensive toxicology studies if used in conjunction with the toxicology data discussed in this document.

[1/] This column specifies the use sites for which the data are required using the following codes: A= Domestic outdoors; B= Greenhouse; C= Tree fruit and nut crop; D= Field and vegetable crop; E= Aquatic food use (watercress); F= Forestry use.

DATA REQUIREMENTS CHART A

ENDOSULFAN

Generic Data Requirements: RESIDUE CHEMISTRY

Name of Test	Composition	Does EPA have data to Partially or Totally Satisfy this Requirement?	Bibliographic Citation	Must additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, when?
Metabolism in Plants	Radiolabeled Active Ingredient	Yes	00003600, 00003642, 00003654 05018169, 05004385, 05004620 05002565, 05003004, 05003801 05003336, 05003085	No
Metabolism in Animals	Radiolabeled Active Ingredient	Yes	00003838, 05003877, 00003743 05003222, 00003742, 00003840	No
Analytical Methods	Technical Grade of Active Ingredient	Yes	00003795, 00003959, 00003703 00003840, 05003395, GS014024	No
Residue Data: Crops				
Alfalfa (fresh)	Technical Grade of Active Ingredient	Yes	00003834, 00003836, 00004258 00003835, 00003841	Yes/26 months[1/]
Alfalfa hay	"	Yes	00003834, 00003836, 00004258 00003835, 00003841	No
Almonds	"	Yes	00004254, 00003612	No
Almond hulls	"	Yes	00004254, 00003713, 00003612	No
Apples	"	Yes	00003787	Yes/26 months[2/]
Apricots	"	Yes	00003789, 00003784	No
Artichokes	"	No	-	Yes/26 months[3/]
Beans	"	Yes	00003796	No
Blueberries	"	Yes	00003587, 00003788, 00003843	No
Broccoli	"	Yes	00003796	No[4/]
Brussels sprouts	"	Yes	00003796	No
Cabbage	"	Yes	00003790	No
Carrots	"	Yes	00003796	No
Cauliflower	"	Yes	00003796	No
Celery	"	Yes	00003796	Yes/26 months[5/]
Cherries	"	Yes	00003782	Yes/26 months[6/]
Collards	"	Yes	00003796	No
Cottonseed	"	Yes	00003725, 00003726, 00003777	No
Cucumbers	"	No	-	Yes/26 months[7/]
Eggplants	"	No	-	Yes/26 months[7/]
Filberts	"	Yes	00004254	No

1/ Residue data on alfalfa seed screening used as animal feed is necessary to determine the contribution to milk and meat.

2/ Residue data on apple pomace is necessary to determine if endosulfan concentrates in pomace used as animal feed.

3/ There are no available adequate residue data for total endosulfan on artichokes at the time of harvest, i.e. 7 days after last application. Residue data by an adequate analytical method capable of determining residues of endosulfan sulfate are required.

4/ There is no available adequate residue data on brocolli, however, the estimation of residues may be based upon data available for another similar crop, such as brussels sprouts and cauliflower.

5/ Residue data at four day treatment to harvest interval is required.

6/ Residue data for the emulsifiable concentrate formulation is required.

7/ There are no available adequate residue data using an adequate analytical method capable of determining total endosulfan residues. None of the methods submitted have been shown to be adequate for the analysis of endosulfan sulfate, and these residue data are not adequate to support the established tolerance, therefore residue data by an analytical method capable of determining residues of endosulfan sulfate are required.

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RESIDUE CHEMISTRY CONTINUED

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Name of Test	Composition	Does EPA have data to Partially or Totally Satisfy this Requirement?	Bibliographic Citation	Must additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, when?
Grapes	Technical Grade of Active Ingredient	Yes	00003788	Yes/26 months[1/]
Kale	"	Yes	00003796	No
Lettuce	"	Yes	00003790, 00003722,	Yes/26 months[2/]
Macadamia Nuts	"	Yes	00004254	No
Melons	"	No	-	Yes/26 months[3/]
Mustard greens	"	Yes	00003796	No
Mustard seed	"	Yes	00003724	No
Nectarines	"	Yes	00003789, 00003784	No
Peaches	"	Yes	00003789, 00003784	No
Pears	"	Yes	00003862	No
Peas (succulent type)	"	Yes	00003949, 00003917	No
Pecans	"	Yes	00004254	No
Peppers	"	Yes	00003864	No
Pineapples	"	Yes	00003797, 00003798, 00003799	Yes/26 months[4/]
Plums	"	Yes	00003786, 00003791	No
Potatoes	"	Yes	00003709	No
Prunes	"	Yes	00003786, 00003791	No
Pumpkins	"	No	-	Yes/26 months[3/]
Rape seed	"	Yes	00003724	No
Safflower seed	"	Yes	00003727	No
Spinach	"	Yes	00003796	No
Strawberries	"	Yes	00003785	No
Grains of: barley, oats, rye and wheat	"	Yes	00003710	No
Straw of: barley, oats, rye and wheat	"	Yes	00003710	No
Sugarbeets	"	Yes	00003730, 00003728	No
Sugarcane	"	Yes	00003901, 00003676	No
Summer squash	"	No	-	Yes/26 months[3/]
Sunflower seed	"	Yes	00003796	No
Sweet corn	"	Yes	00003634, 00003760	No
Sweet potatoes	"	Yes	00003642, 00003569	No
Tea	"	Yes	00003756, 00003744	No
Tomatoes	"	Yes	00003783	Yes/26 months[5/]
Turnip greens	"	Yes	00003796	No
Walnuts	"	Yes	00004254	No
Watercress	"	Yes	00003796	No
Winter squash	"	No	-	Yes/26 months[3/]

1/ Residue data for grape pomace and raisin waste are necessary to determine the contribution of this animal feed item to milk and meat.

2/ Residue data on untrimmed heads of lettuce are needed.

3/ There are no available adequate residue data using an adequate analytical method capable of determining total endosulfan residues. None of the methods submitted have been shown to be adequate for the analysis of endosulfan sulfate, and these residue data are not adequate to support the established tolerance, therefore residue data by an analytical method capable of determining residues of endosulfan sulfate are required.

4/ Residue data on pineapple bran are necessary to determine its contribution as an animal feed item to milk and meat.

5/ Residue data for an adequate number of tomato samples are required to establish the expected range of residues.

RESIDUE CHEMISTRY CONTINUED

Name of Test	Composition	Does EPA have data to Partially or Totally Satisfy this Requirement?	Bibliographic Citation	Must additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, when?
Residue Data: Animal Foodstuffs				
Alfalfa (fresh)	Technical Grade of Active Ingredient	Yes	00003834, 00004258, 00003835 00003841	No
Alfalfa (hay)	"	Yes	(same as for fresh alfalfa)	No
Almond hulls	"	Yes	00004254, 00003612, 00003713	No
Apple pomace	"	No	-	Yes/26 months[2/]
Beans (vines, forage, fodder)	"	No	-	No[1/]
Carrots	"	No	-	No[1/]
Cottonseed (meal, forage, fodder)	"	No	-	No[1/]
Grain of: barley, oats, rye and wheat	"	No	-	No[1/]
Grape pomace (and raisin waste)	"	No	-	Yes/26 months[2/]
Nectarine pomace	"	No	-	No[1/]
Peach pomace and waste	"	No	-	No[1/]
Peas, succulent (vine, forage and fodder)	"	No	-	No[1/]
Pineapple bran	"	No	-	Yes/26 months[2/]
Straw of: barley, oats rye and wheat	"	No	-	No[1/]
Sugar beets (tops and dried pulp	"	Yes	00003728	No
Sugarcane (bagasse and dried pulp)	"	Yes	00003901, 00003676, 00003796	No[1/]
Sunflower seed meal	"	Yes	00003796	No
Sweet corn waste	"	Yes	00003760	No[3/]
Tomato pomace	"	No	-	Yes/26 months[2/]
Residue Data: Meat	"	Yes	00003838, 00003743, 00003742 00003877, 05003222, 05013696	No
Milk	"	Yes	00003838, 00003743, 05003877 05003222, 05013696	No
Poultry	"	Yes	00003840	No

1/ Label restrictions prohibit the use of this commodity as animal feed, therefore residue data are not being required. In order to remove label restrictions, i.e., allow use of this commodity for animal feed or food, appropriate residue data showing the nature and the amount of expected residues are necessary.

2/ The Agency has concluded that restrictions against feeding this commodity to animals is impractical, in that the grower has no control over the disposition of this commodity's by-products. Residue data are required to determine if there are endosulfan residues in this by-product and to determine if a food additive tolerance is needed.

3/ Husklage from processing or canning cannot be fed to livestock per label restrictions.

DATA REQUIREMENTS CHART A

ENDOSULFAN

Generic Data Requirements: ECOLOGICAL EFFECTS

Guidelines Citation	Name of Test	When Required[1]	Composition	Does EPA have data to partially or totally satisfy this requirement?	Bibliographic Citation	Must additional data be submitted under FIFRA 3(c)(2)(B)? If so, due when?
163.71-1	**Avian Single-Dose Oral LD_{50}**	A,C,D,E,F	Technical Grade of Active Ingredient	Partially	05003462, GS014015	Yes/8 months[2]
163.71-2	Avian Dietary LC_{50}	A,C,D,E,F	"	Yes	00022923	No
163.71-4	Avian Reproduction	A,C,D,E,F	"	No	-	Yes/14 months
163.72-1	Fish Acute LC_{50}	A,C,D,E,F	"	Partially	GS014012, 05003107 GS014014, 05014941	Yes/14 months[3]
163.72-2	Acute Toxicity to Aquatic Invertebrates	A,C,D,E,F,	"	Yes	05008271, 05017538 05009242	No
163.72-3	Acute Toxicity to Estuarine & Marine Organisms	C,D,E	"	Partially	00001328, 05000819 05005824, 05003062	Yes/8 months[4]
163.72-4	**Fish Early Life-Stage Aquatic Invertebrate Life Cycle**		"	Partially	05008271	Reserved[5]
163.72-5	**Fish Life-cycle**					Reserved[5]
163.72-6	**Aquatic Organism**					Reserved[5]

These data requirements are current as of March, 1982. Refer to the guidance package for updated requirements.

[1] This column specifies the use sites for which the data are required using the following codes: A= Domestic outdoors; B= Greenhouses; C= Tree fruit and nut crops; D= Field and vegetable crops; E= Aquatic food use (watercress); F= Forestry use.

[2] The dose response data were not provided by the acute oral studies reviewed, therefore no statistical evaluation was possible.

[3] The submitted studies on coldwater fish did not provide dose response data nor the percentage of active ingredient tested, therefore no statistical evaluation could be performed, nor could the generic status be confirmed. Since the available data on formulation testing indicate coldwater fish are more sensitive to endosulfan's effects than warmwater fish or aquatic invertebrates, the coldwater 96 hour LC_{50} is essential to the hazard assessment.

[4] The submitted tests partially fulfill this requirement because they provided information on the acute toxicity to fish and shrimp. However, additional studies must be submitted on the crab and mollusc.

[5] This requirement is reserved pending the evaluation of required environmental fate data.

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DATA REQUIREMENTS CHART B

ENDOSULFAN

Product-Specific Manufacturing-Use Data Requirements: PRODUCT CHEMISTRY

Guidelines Citation	Name of Test	Composition	Does EPA have data to partially or totally satisfy this requirement?	Bibliographic Citation	Must additional data be submitted under FIFRA 3(c)(2)(B)? If so, due when?
163.61-3	Product Identity and Disclosure of Ingredients	Each Product	Partially		Yes[1]
163.61-4	Description of Manufacturing Process	Each Product	Partially		Yes[1]
163.61-5	Discussion on Formation of Unintentional Ingredients	Each Product	No		Yes[1]
163.61-6	Declaration & Certification of Ingredients Limits	Each Product	Partially		Yes[1]
163.61-7	Product Analytical Methods and Data	Each Product	Yes	00003657, 00003794	No
163.64-2	Color	Each Product[2]	Partially		Yes[1]
163.64-3	Physical State	Each Product[3]	Partially		Yes[1]
163.64-4	Odor	Each Product[2]	Partially		Yes[1]
163.64-5	Melting Point	Each Product[2]	Partially		Yes[1]
163.64-7	Density or Specific Gravity	Each Product[3]	Partially		Yes[1]
163.64-8	Solubility	Each Product[2]	Partially		Yes[1]
163.64-9	Vapor Pressure	Each Product[3]	Partially		Yes[1]

These data requirements are current as of March, 1982. Refer to the guidance package for updated requirements.

1/ These requirements must be fulfilled by each applicant. Data from other applicants may not be cited. Therefore, even if the requirements have been partially or completely fulfilled for some products, no references are given. These requirements must be filled at the time of registration or reregistration.

2/ If the manufacturing use product is a formulation intermediate, then data must be submitted on the technical used to manufacture the intermediate.

3/ If the manufacturing use product is a formulation intermediate, then data must be submitted on the technical used to manufacture the intermediate and on the intermediate itself.

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PRODUCT CHEMISTRY CONTINUED

Guidelines Citation	Name of Test	Composition	Does EPA have data to partially or totally satisfy this requirement?	Bibliographic Citation	Must additional data be submitted under FIFRA 3(c)(2)(B)? If so, due when?
163.64-11	Octanol/water Partition	Each Product[2]	No		Yes[1]
163.64-12	pH	Each Product[3]	No		Yes[1]
163.64-13	Stability	Each Product[2]	Partially		Yes[1]
163.64-14	Oxidizing/Reducing Action	Each Product	No		Yes[1]
163.64-15	Flammability	Each Product	Partially		Yes[1]
163.64-16	Explosiveness	Each Product	Partially		Yes[1]
163.64-17	Storage Stability	Each Product	Partially		Yes[1]
163.64-18	Viscosity	Each Product	Partially		Yes[1]
163.64-19	Miscibility	Each Product	No		Yes[1]
163.64-20	Corrosiveness	Each Product	Partially		Yes[1]

These data requirements are current as of March, 1982. Refer to the guidance package for updated requirements.

1/ These requirements must be fulfilled by each applicant. Data from other applicants may not be cited. Therefore, even if the requirements have been partially or completely fulfilled for some products, no references are given. These requirements must be filled at the time of registration or reregistration.
2/ If the manufacturing use product is a formulation intermediate, then data must be submitted on the technical used to manufacture the intermediate.
3/ If the manufacturing use product is a formulation intermediate, then data must be submitted on the technical used to manufacture the intermediate and on the intermediate itself.

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DATA REQUIREMENTS CHART C

ENDOSULFAN

End-Use Product-Specific Data Requirements: PRODUCT CHEMISTRY

Guidelines Citation	Name of Test	Composition	Does EPA have data to partially or totally satisfy this requirement?	Bibliographic Citation	Must additional data be submitted under FIFRA 3(c)(2)(B)? If so, due when?
163.61-3	Product Identity & Disclosure of Ingredients	Each Product	Partially		Yes1/
163.61-4	Description of Manufacturing Process	Each Product	No		Yes1/
163.61-5	Discussion on Formulation of Unintentional Ingredients	Each Product	No		Yes1/
163.61-6	Declaration & Certification of Ingredients Limits	Each Product	Partially		Yes1/
163.61-7	Product Analytical Methods & Data	Each Product	Yes		No
163.64-2	Color	Each Product	No		Yes1/
163.64-3	Physical State	Each Product	Yes		No
163.64-4	Odor	Each Product	No		Yes1/
163.64-7	Density or Specific Gravity	Each Product	Partially		Yes1/
163.64-12	pH	Each Product	No		Yes1/
163.64-14	Oxidizing/Reducing Action	Each Product	No		Yes1/
163.64-15	Flammability	Each Product	No		Yes1/
163.64-16	Explosiveness	Each Product	No		Yes1/
163.64-17	Storage Stability	Each Product	Partially		Yes1/
163.64-18	Viscosity	Each Product	No		Yes1/
163.64-19	Miscibility	Each Product	No		Yes1/
163.64-20	Corrosiveness	Each Product	Partially		Yes1/

These data requirements are current as of March, 1982. Refer to the guidance package for updated requirements.

1/ These requirements must be fulfilled by each applicant. Data from other applicants may not be used. Therefore, even if the requirement has been partially or completely fulfilled for some products, no references are given. These requirements must be filled at the time of registration or reregistration.

DATA REQUIREMENTS CHART C

ENDOSULFAN

Product-Specific End-Use Data Requirements: TOXICOLOGY

Guidelines Citation	Name of Test	Composition	Does EPA have data to partially or totally satisfy this requirement?	Bibliographic Citation	Must additional data be submitted under FIFRA 3(c)(2)(B)? If so, due when?
163.81-1	Acute Oral Toxicity	Each Product1/	No	-	Yes/8 months
163.81-2	Acute Dermal Toxicity	Each Product1/	No	-	Yes/8 months
163.81-3	Acute Inhalation Toxicity	Each Product2/	No	-	Yes/8 months
163.81-4	Primary Eye Irritation	Each Product3/	No	-	Yes/8 months
163.81-5	Primary Skin Irritation	Each Product4/	No	-	Yes/8 months

These data requirements are current as of March, 1982. Refer to the guidancepackage for updated requirements.

1/ Testing is required for representatives of the following formulations: dust (5 and 25%), wettable powder (50%), and emulsifiable concentrate (9, 22-24, and 50%).

2/ Testing is required for representatives of the following formulations: dust (5 and 25%), wettable powder (50%), Impregnated material (15%) and pressurized liquid (aerosol 10%).

3/ Testing is required for representatives of the following formulations: dust (5 and 25%), grannular (3%), wettable powder (50%), and emulsifiable concentrate (9, 22-24, and 50%).

4/ Testing is required for representatives of the following formulations: dust (5 and 25%), wettable powder (50%), emulsifiable concentrate (9, 22-24, and 50%), and pressurized liquid (aerosol 10%).

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DATA REQUIREMENTS CHART C

ENDOSULFAN

Product-Specific End-Use Data Requirements: ECOLOGICAL EFFECTS

Guidelines Citation	Name of Test	Composition	Does EPA have data to partially or totally satisfy this requirement?	Bibliographic Citation	Must additional data be submitted under FIFRA 3(c)(2)(B)? If so, due when?
163.71-5	Simulated and Actual Field Testing for Mammals and Birds				Reserved[1]
163.72-1	Fish Acute LC_{50}	Representative Products of 35EC, 50WP, and 4D	Partially	GS014011, GS014010 05003103, 05004797 05003351	Yes/8 months[2] [4]
163.72-2	Acute Toxicity to Aquatic Invertebrates	Representative Products of 35EC, 50WP, and 4D	No	-	Yes/8 months[4]
163.72-3	Acute Toxicity to Estuarine and Marine Organisms	Representative Products of 35EC, 50WP and 4D	No	-	Yes/8 months[4]
163.72-6	Simulated or Actual Field Testing For Aquatic Organisms				Reserved[3]

These data requirements are current as of March, 1982. Refer to the guidance package for updated requirements.

1/ If adverse effects are demonstrated by testing under 163.71-4, expected field residue information will be evaluated to determine whether data should be conditionally required under 163.71-5 to demonstrate effects of formulations on avian survival and reproduction.

2/ The data requirement is only partially satisfied for the 35EC formulation because no information was given in the studies other than to indicate that the test material was a 35EC. This is not sufficient test material identification, as other inerts or additives are presumed to be a part of this formulation. Ultimate identification of formulations for which this requirement (163.72-1) is satisfied will be accomplished by comparing "Confidential Statements of Formula" received with registration applications, to the Data Evaluation Records of the submitted formulated product studied in the Agency's files.

3/ This requirement is reserved pending the evaluation of required environmental fate data.

4/ This data requirement applies only to the watercress use pattern.

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INDEX OF CITATIONS USED IN THE DATA REQUIREMENTS CHARTS
REFERENCES LISTED IN NUMERICAL ORDER

MRID	CITATION
00001328	Earnest, R. (1970)
00003587	Shuttleworth, J.M. (1971)
00003600	FMC Corporation (1958)
00003603	Keller, J.G. (1959)
00003604	Keller, J.G. (1959)
00003612	FMC Corporation (19??)
00003634	Stanovick, R.P. (1967)
00003642	FMC Corporation (1964)
00003654	Ware, G.W. et al. (1961)
00003657	Hooker Chemical Corporation (1964)
00003669	Stanovick, R.P. (1965)
00003676	FMC Corporation (1964)
00003693	Elsea, J.R. (1957)
00003703	FMC Corporation (19??)
00003709	FMC Corporation (1969)
00003710	FMC Corporation (1970)
00003711	Arnold, D. (1972)
00003713	FMC Corporation (1971)
00003722	Hinstridge, P.A. (1966)
00003724	Winterlin, W. (1968)
00003725	FMC Corporation (1966)
00003726	FMC Corporation (1969)
00003727	FMC Corporation (1967)
00003728	Shuttleworth, J.M. (1971)
00003730	FMC Corporation (1970?
00003742	Maier-Bode, H. (1966)
00003743	Gorbach, S (1965)
00003744	Gorbach, S. (1973)
00003756	American Hoechst Corporation (1968)
00003760	Hinstridge, P.A. (1968)
00003761	Chin, W.T.; Stanovick, R.P. (1964)
00003762	Palazzolo, R.J. (1964)
00003777	Stanovick, R.P. (1964)
00003782	Stanovick, R.P. (1963)
00003783	Stanovick, R.P. (1964)
00003784	Stanovick, R.P. (1965)
00003785	Hinstridge, P.A. (1963)
00003786	Hinstridge, P.A. (1963)
00003787	Hinstridge, P.A. (1963)
00003788	Hinstridge, P.A. (1963)
00003789	Hinstridge, P.A. (1963)
00003790	Hinstridge, P.A. (1963)
00003791	Hinstridge, P.A. (1964)
00003794	Velsicol Chemical Corporation (1974)
00003795	Cassil, C.C.; Drummond, P.E. (1965)
00003796	FMC Corporation (1965)
00003797	Hinstridge, P.A. (1966)
00003798	Thornburg, W. (1966)

MRID	CITATION
00003799	Thornburg, W. (1966)
00003800	Stanovick, R.P. (1966)
00003834	Hinstridge, P.A. (1964)
00003835	Hinstridge, P.A. (1965)
00003836	Stanovick, R.P. (1964)
00003838	Stanovick, R.P. (1965)
00003840	Stanovick, R.P. (1967)
00003841	Ware, G.W. (1967)
00003843	FMC Corporation (1971)
00003862	Hinstridge, P.A. (1971)
00003864	Hinstridge, P.A. (1966)
00003877	Keller, J.C. (1958?)
00003901	FMC Corporation (1964)
00003917	FMC Corporation (1965)
00003949	FMC Corporation (1965)
00003959	FMC Corporation (19??)
00004254	FMC Corporation (1967)
00004257	Deema, P. et al. (1966)
00004258	Stanovick, R.P. (1964)
00022923	Hill, E.F. et al. (1975)
05000819	Korn, S.; Earnest, R. (1974)
05002183	Boyd, E.M. et al. (1970)
05002565	Beard, J.E.; Ware, G.W. (1969)
05002841	Archer, T.E. et al. (1972)
05003004	Chopra, N.M.; Mahfouz, A.M. (1977)
05003007	Martens, R. (1976)
05003053	Ernst, W. (1977
05003062	Roberts, D. (1975)
05003085	Kavadia, V.S. et al. (1978)
05003103	Amminikutty, C.K.; Rege, M.S. (1977)
05003107	Macek, K.J. et al. (1969)
05003222	Gorbach, S.G. et al. (1968)
05003336	Stewart, D.K.R.; Cairns, K.G. (1974)
05003351	Reddy, T.G.; Gomathy, S. (1977)
05003395	Burke, J.; Mills, P.A. (1963)
05003462	Hudson, R.H. et al. (1972)
05003471	El Zorgani, G.A.; Omer, M.E.H. (1974)
05003503	Gupta, P.K.; Ehrnebo, M. (1979)
05003703	Dorough, H.W. et al. (1978)
05003718	Gupta, P.K.; Chandra, S.V. (1975)
05003801	Chopra, N.M.; Mahfouz, A.M. (1977)
05003877	Frank, R. et al. (1975)
05004262	Peeters, J.F. et al. (1975)
05004385	Terranova, A.C.; Ware, G.W. (1963)
05004617	Rao, M.V.R.; Rana, R.S. (1977)
05004620	Harrison, R.B. et al. (1967)
05004797	Frick, K.E. (1959)
05005047	Martens, R. (1977)
05005315	Martens, R. (1972)
05005824	Schimmel, S.C. et al. (1977)

MRID	CITATION
05007464	Schuphan, I. et al. (1968)
05007645	Ely, T.S. et al. (1967)
05008271	Macek, K.J. et al. (1976)
05009242	Sanders, H.O. (1969)
05010061	Roy, P. et al. (1975)
05012725	Miles, J.R.W.; Moy, P. (1979)
05013674	Bandyopadhyay, S. et al. (1979)
05013696	Oeser, H. (1970
05013707	Spiro, S.; Trevisani, G.R. (1974)
05014941	Pickering, Q.H.; Henderson, C. (1966)
05017001	Gaikawad, S.T. et al. (1973)
05017538	Sanders, H.O. (1972)
05018169	Terranova, A.C. (1962)
05019845	Strachan, W.M.J.; Huneault, H. (1979)
GS014001	Reno, F.E. (1975)
GS014003	Reno, F.E. (1975)
GS014004	Reno, F.E. (1975)
GS014005	Reno, F.E. (1976)
GS014007	Gains, T.B. (1969)
GS014008	Raltech Scientific Services (1981)
GS014009	Fahrig, R. (1974)
GS014010	Ludeman, J.A. (1972)
GS014011	U.S.E.P.A. (1976)
GS014012	U.S.E.P.A. (1976)
GS014014	Buccafusco, R.J.; Sleight, B.H. (1976)
GS014015	Schafer, E.W. (1972)
GS014023	Raltech Scientific Services (1981)
GS014024	Gunther, F.A. (1951)

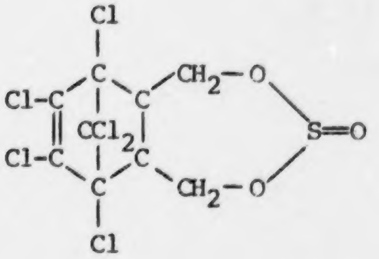
IV. PRODUCT CHEMISTRY

A. Chemical Identity
B. Manufacturing Process
C. Formation of Unintentional Ingredients
D. Ingredient Limits in Endosulfan Products
E. Product Analytical Methods and Data
F. Physical and Chemical Properties
G. Summary of Data Gaps

A. CHEMICAL IDENTITY

In the United States, the American National Standards Institute (ANSI) approved common name for hexachlorohexahydromethano-2,4,3-benzodioxathiepin 3-oxide is "endosulfan". The Chemical Abstracts Service Collective Indexes list the names as 6,7,8,9,10,10-hexachloro-1,5,5a,6,9,9a-hexahydro-6,9-methano-2,4,3-benzodioxathiepin 3-oxide (9CI) and 1,4,5,6,7,7-hexachloro-5-norbornene-2,3-dimethanol cyclic sulfite (8CI). Endosulfan is also commonly known by the trade name "Thiodan" and by numerous other names. The Chemical Abstracts Registry number (CAS) is 115-29-7, and the EPA Shaughnessy number is 079401. Endosulfan is a mixture of two geometric isomers (endosulfan I and II), a synthetic cyclodiene, that was introduced in 1956 as an experimental broad spectrum pesticide.

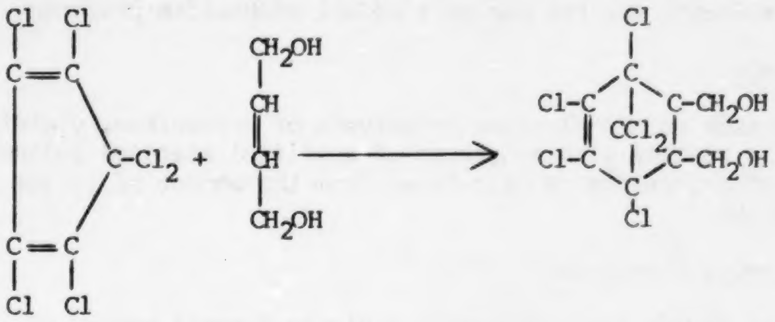
The structural formula is:



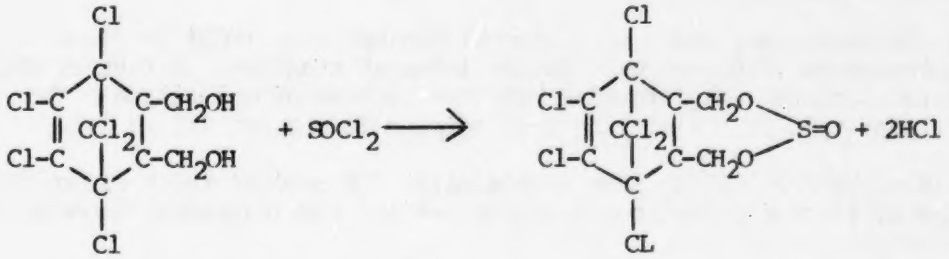
B. MANUFACTURING PROCESS

The synthesis process for endosulfan can be found in U.S. Patent No. 2,799,685 which is held by Farbwerke Hoechst, AG (1957). The Pesticide Manufacturing and Toxic Materials control Encyclopedia (Sittig, 1980) outlines the following manufacturing process.

The first step consists of a Diels-Alder condensation of hexachlorocyclopentadiene (hex) with 2-butene-1,4-diol to form the corresponding adduct.



In the second step this adduct is reacted with thionyl chloride to form the endosulfan product.



Hooker Chemical (19??, MRID 00003658) and Velsicol (1975, MRID 00003793) describe similar processes. Further manufacturing details are considered to be trade secret information, and cannot be elucidated in this standard.

C. FORMATION OF UNINTENTIONAL INGREDIENTS

No theoretical discussions have been submitted, nor could be found, on possible contaminants in the technical materials (other than those listed in the Confidential Statements of Formula) nor in any of the end-use products. Little information is available on the formulating processes of end-use products.

D. INGREDIENT LIMITS IN ENDOSULFAN PRODUCTS

There are four manufacturers of technical endosulfan. They are Food, Machinery and Chemical Corporation (FMC), Hooker Chemical Corporation, Makhteshim Chemical Works (Israel), and Velsicol Chemical Corporation. The technical product ranges from 94-96% active ingredient.

Three companies produce formulation intermediate endosulfan (manufacturing use products) and they are Chevron Chemical Company, FMC, and Makhteshim (Israel).

A commitment (certification) is required from each registrant that the ingredients and impurities in the products will be maintained within specified limits for as long as the product is offered for sale. Upper and lower limits are required for the active and intentionally added inert ingredients. Upper limits are required for the impurities. This information is to be submitted with the Confidential Statement of Formula.

E. PRODUCT ANALYTICAL METHODS AND DATA

The EPA Manual of Chemical Methods for Pesticides and Devices (1976) describes the following methods suitable for the analysis of all endosulfan products.

1. Alkaline Hydrolysis

This determination is based on the alkaline hydrolysis of endosulfan, yielding sodium sulfite. This is reacted with an excess of acidified standard iodine solution. The amount of endosulfan is calculated from the amount of iodine used by the sodium sulfite.

2. Infrared Spectroscopy (tentative)

Samples are dissolved in carbon disulfide which contains a small amount of sodium sulfate.

3. GLC-TCD or GLC-FID (tentative)

Gas-liquid chromatography (GLC) with thermal conductivity (TCD) or flame ionization detectors (FID) are used as the internal standard. A further GLC-FID method (also tentative) determines the two isomers of endosulfan. The ratio of I (alpha) to II (beta) ranges in samples from about 4:1 to 2:1.

Velsicol (1974, MRID 00003794) submitted similar GLC methods (with FID or TCD detectors as above) for detection of endosulfan and the individual isomers in formulated products.

F. PHYSICAL AND CHEMICAL PROPERTIES

1. Color

Pure endosulfan is colorless to white (FMC, 19??, MRID 00003729; Makhteshim, 1969, MRID 00003821; and American Hoechst, 1965, MRID 00003746).

Technical endosulfan ranges in color from light brown or tan to dark brown (FMC, 19??, MRID 00003729; Makhteshim, 1969, MRID 00003821; American Hoechst, 1965, MRID 00003746; Velsicol, 19??, MRID 00003772; and Hooker Chemical, 19??, MRID 00003658).

Two of the formulation intermediates (manufacturing use products) were light brown to brown (Makhteshim, 19??, MRID 00003821).

2. Odor

There is no odor for the pure compound (FMC, 19??, MRID 00003729 and Makhteshim, 1969, MRID 00003821).

The technical compound has a slight odor of sulfur dioxide (FMC, 19??, MRID 00003729; Makhteshim, 1969, MRID 00003821; American Hoechst, 1965, MRID 00003746; and Velsicol, 19??, MRID 00003772).

The manufacturing use products will have the specific odor of the solvent used (Makhteshim, 1969, MRID 00002821).

3. Melting Point

There are two isomers of the pure compound, I (alpha) and II (beta). For isomer I, the melting range is 106-110°C; for isomer II the range is 208-210°C; and the melting range for the technical product is 70-100°C (FMC, 19??, MRID 00003729; Makhteshim, 1969, MRID 00003821; American Hoechst, 1965, MRID 00003746; Velsicol, 19??, MRID 00003772; and Hooker Chemical, 19??, MRID 00003658).

4. Solubility

The following results were reported for the technical product at 20°C, except where noted.

Solvent	Solubility	Reference
xylene	45 g/100 g	FMC, 19??, MRID 00003729
	45-55 g/100 g	American Hoechst, 1965, MRID 00003746
	soluble	Makhteshim, 1969, MRID 00003821
water	0.6 ppm	FMC, 19??, MRID 00003729
	insoluble	Makhteshim, 1969, MRID 00003821
	insoluble	Velsicol, 19??, MRID 00003772
	0.0	Hooker Chemical, 19??, MRID 00003658
	530 ug/l (isomerI)*	Weil et al., 1974, MRID 05012895
	280 ug/l (isomer II)*	Weil et al., 1974, MRID 05012895
	*done at 25°C	
kerosene	20 g/100 g	FMC, 19??, MRID 00003729
	25 g/100 g	American Hoechst, 1965, MRID 00003746
chloroform	50 g/100 g	FMC, 19??, MRID 00003729
	100 g/100 g	American Hoechst, 1965, MRID 00003746
	soluble	Makhteshim, 1969, MRID 00003821
	>150 g/100 g	Hooker Chemical, 19??, MRID 00003658
ethanol	5 g/100 g	FMC, 19??, MRID 00003729
		American Hoechst, 1965, MRID 00003746
	soluble	Makhtshim, 1969, MRID 00003821
	>7.2 g/100 g	Hooker Chemical, 19??, MRID 00003658
methyl chloride	45 g/100 g	FMC, 19??, MRID 00003729
acetone	35 g/100 g	FMC, 19??, MRID 00003729
	50 g/100 g	American Hoechst, 1965, MRID 00003746
	soluble	Makhteshim, 1969, MRID 00003821
benzene	37 g/100 g	FMC, 19??, MRID 00003729
	59 g/100 g	American Hoechst, 1965, MRID 00003746

4. Solubility (continued)

Solvent	Solubility	Reference
carbon tetrachloride	29 g/100 g	FMC, 19??, MRID 00003729
	29 g/100 g	American Hoechst, 1965, MRID 00003746
	81.8 g/100 g	Hooker Chemical, 19??, MRID 00003658
alkylbenzenes (Solvesso 100)	25 g/100 g	FMC, 19??, MRID 00003729
	25 g/100 g	American Hoechst, 1965, MRID 00003746
methanol	11 g/100 g	FMC, 19??, MRID 00003729
	11.9 g/100 g	Hooker Chemical, 19??, MRID 00003658
	11 g/100 g	American Hoechst, 1965, MRID 00003746
toluene	57 g/100 g	American Hoechst, 1965, MRID 00003746
	>150 g/100 g	Hooker Chemical, 19??, MRID 00003658
amyl acetate	53 g/100 g	American Hoechst, 1965, MRID 00003764
fuel oil	14 g/100 g	American Hoechst, 1965, MRID 00003746
methylene chloride	45 g/100 g	American Hoechst, 1965, MRID 00003746
acetic acid	18 g/100 g	Hooker Chemical, 19??, MRID 00003658
dioxane	>150 g/100 g	Hooker Chemical, 19??, MRID 00003658
chlorobenzene	>150 g/100 g	Hooker Chemical, 19??, MRID 00003658
heptane	16.5 g/100 g	Hooker Chemical, 19??, MRID 00003658

5. Stability

In the presence of acids, alkalis, and moisture, pure and technical endosulfan will decompose to sulfur dioxide and endosulfan alcohol (FMC, 19??, MRID 00003729; Makhteshim, 1969, MRID 00003821; American Hoechst, 1965, MRID 00003746; and Velsicol, 19??, MRID 00003772).

6. Physical State

The technical and pure forms are crystalline solids (FMC, 19??, MRID 00003729; Makhteshim, 1969, MRID 00003821; American Hoechst, 1965, MRID 00003746; Velsicol, 19??, MRID 00003772; and Hooker Chemical, 19??, MRID 00003658).

7. Density or Specific Gravity

The apparent density in xylene at 20°C is 1.745 (FMC, 19??, MRID 00003729; American Hoechst, 1965, MRID 00003746; and Velsicol, 19??, MRID 00003772).

The density of the emulsifiable concentrate formulation intermediate (35%) is 1.10-1.11 at 20°C (Makhteshim, 1969, MRID 00003821).

8. Vapor Pressure

There is no measurable vapor pressure at 20-75°C (FMC, 19??, MRID 00003729; American Hoechst, 1965, MRID 00003746; and Makhteshim, 1969, MRID 00003821).

At 80°C, FMC (19??, MRID 00003729) reports that the vapor pressure of the technical material is .009mm Hg.

9. Storage Stability

Makhteshim, 1969, MRID 00003821) reports that the 35% emulsifiable concentrate and the 50% wettable powder formulation intermediates are stable when kept in intact containers.

10. Flammability

Makhteshim (1969, MRID 00003821) reports that the pure compound and the 50% wettable powder formulation intermediate are nonflammable.

11. Explosiveness

Velsicol (19??, MRID 00003772) reports that there is no explosive hazard for the technical material.

12. Viscosity

Hooker Chemical (19??, MRID 00003658) reports that at 210°C, the technical has a viscosity of 231.3 centistrokes=49.47.

13. Corrosion Characteristics

Makhteshim, 1969, MRID 00003821) reports that the pure and technical compounds and the 35% emulsifiable concentrate formulation intermediate is corrosive to iron.

G. SUMMARY OF DATA GAPS

Data requirements for product identity, description of manufacturing process, certification of ingredient limits, and physical/chemical properties may have been partially satisfied for technical and manufacturing use endosulfan. The registrants have not discussed the formation of unintentional ingredients. The Agency requires submission of this information.

V. ENVIRONMENTAL FATE

A. Use Summary
B. Environmental Fate Profile
C. Exposure Profile
D. Summary of Data Gaps

A. USE SUMMARY

Endosulfan is a nonsystemic insecticide with contact and stomach action which is federally registered for use on a large number of agricultural and ornamental crops. Approximately 60-80 percent of the pesticide is used on fruit trees (apples, peaches, pears and cherries) and vegetables (potatoes, tomatoes, green beans, lettuce and sweet corn). Other use sites consist primarily of cotton, alfalfa, tobacco, sugar beets, artichokes, grapes, plums, prunes and pecans. Use of endosulfan on cotton, which occurs primarily in the southwestern United States, varies from year to year.

Endosulfan is used on potatoes in the northeastern and north central states for the control of aphids, flea beetles and Colorado potato beetles; apples in the north central states for the control of aphids and white apple leafhoppers; tomatoes in California and the southeastern states for control of aphids, flea beetles and lepidopteran larvae; lettuce in the southwestern states for control of stink bugs and occasionally lepidopteran larvae. Endosulfan is also registered for use on watercress to control Cyclamen mites.

Endosulfan is manufactured into 96, 95 and 94% technical products. The formulation intermediates include 50 and 35% wettable powders, 35% emulsifiable concentrate, and 25% dust concentrate formulations. Endosulfan is formulated for end use into 2, 4, and 5% dusts; 3% granules; 50% wettable powders; 9, 22-24, and 33-34% emulsifiable concentrates; 10% pressurized liquids (aerosol); and a 15% impregnated material (pressure fumigant). The emulsifiable concentrate and wettable powder end use formulations are diluted with water and applied predominately as foliar applications by aircraft and ground equipment. Endosulfan is compatible with most other pesticides except lime sulfur and other strong alkaline chemicals.

It is estimated that the domestic use of endosulfan totals 1.5 to 2 million pounds of the active ingredient annually.

B. ENVIRONMENTAL FATE PROFILE

The available data are insufficient to completely assess the environmental fate of endosulfan.

Sterile controls of metabolism studies (Miles and Moy, 1979, MRID 05012725; Martens, 1976, MRID 05003007; and Martens, 1972, MRID 05005315) clearly demonstrate that physico-chemical hydrolysis of the ester linkage of endosulfan occurs. Endosulfan was hydrolyzed after six week's incubation at 27°C to endosulfan diol with a strong dependence on the pH (the values ranged from 1 percent hydrolysis occurring at pH 4.3 to 90 percent at pH 8 or above). However, additional data will be required on the hydrolysis properties of endosulfan, since these properties were not fully detailed.

Preliminary data (Archer et al., 1972, MRID 05002841) show that undiluted endosulfan (endosulfan I and II isomers) has a photolytic half-life of approximately seven days. The primary photolysis product is endosulfan diol, which is further photodegraded to endosulfan alpha-hydroxyether and an unidentified metabolite with a half-life of approximately seven days. Endosulfan alpha-hydroxyether and endosulfan ether were photodegraded (11-30 percent) to endosulfan lactone. Endosulfan lactone and endosulfan sulfate are stable to light. Since the analysis for photolysis products was conducted only once, additional data are required on the rate of endosulfan degradation.

In general, endosulfan and its metabolites appear to persist in soil. When applied to aerobic or anaerobic soil, 21-59 percent and 55-69 percent, respectively, of the endosulfan remained 15 weeks after treatment (Martens, 1977, MRID 05005047). Endosulfan is oxidized to its major transformation product, endosulfan sulfate.

In flooded soil (Martens, 1977, MRID 05005047), the rate of endosulfan degradation was slower than under aerobic conditions but faster than under anaerobic conditions. Hydrolysis to endosulfan diol was the major transformation, however, some oxidation to endosulfan sulfate did occur. The data from this anaerobic soil study are insufficient to determine the rate of formation and decline of endosulfan metabolites.

When added to cultures of 59 soil bacteria species (including actinomyces) and 28 species of soil fungi, endosulfan was transformed by approximately one-fourth of the bacteria and over half of the fungi (Martens, 1976, MRID 05003007; and Martens, 1972, MRID 05005315). The degradative pathway appeared to be pH dependent. At pH 6.5 or above, hydrolysis of endosulfan to endosulfan diol appears to be the predominant reaction. The process is probably physico-chemical but appeared to be accelerated by microbes, either by the enzymatic reactions or by induced changes in pH. Endosulfan diol oxidized to endosulfan alpha-hydroxyether, which oxidized to endosulfan lactone. These processes occur under sterile as well as nonsterile conditions but at a slower rate under sterile conditions. Endosulfan lactone transformed to unspecified products at equal rates under sterile and nonsterile conditions, thus indicating that its breakdown is a physico-chemical process. At pH's below 6.5, endosulfan primarily oxidized to endosulfan sulfate. This occurred only under nonsterile conditions. Some endosulfan sulfate hydrolyzed to endosulfan diol (Miles and Moy, 1979, MRID 05012725; Martens, 1976, MRID 05003007; and Martens, 1972, MRID 05005315).

Endosulfan had no effect on ammonification and stimulates nitrification (Gaikawad et al., 1973, MRID 05017001). The effect on nitrogen fixation is unclear because endosulfan stimulated the growth of Azobacter vinelandii by 100 percent but reduced it nitrogenase activity by 77 percent (Peeters et al., 1975, MRID 05004262). Thus the inhibition of nitrogen-fixing capacity of A. vinelandii by endosulfan might be offset by increases in its growth. Seven symbiotic Rhizobium species were not inhibited in vitro by 0.2% endosulfan; however, R. leguminosarum was slightly inhibited (Bandyopadhyay et al., 1979, MRID 05013674). Endosulfan applied at 20-38 kg/ha (18-24 lb/A) to soil initially inhibited the soil microbial population. The microbial population was able to recover within 20 days. The application rate was in excess of the application rates recommended in the use patterns, therefore, it is possible that there would be no initial inhibition of the microbial populations (Roy et al., 1975, MRID 05010061).

Data from a photolysis study (Archer et al., 1972, MRID 05002841) demonstrated that endosulfan and its metabolites volatilized when directly exposed to sunlight. More than 50 percent of the applied endosulfan or individual metabolites may be lost by volatilization after severe exposure for seven days. Monitoring studies also show that endosulfan volatilizes. Spiro and Trevisani (1974, MRID 05013707) found endosulfan background levels of up to 25 ng/m^3 in Italy in 1973. Strachan and Huneault (1979, MRID 05019845) found endosulfan I and II residues in some rain and snow samples collected in the Great Lakes region in Ontario in 1976. Although the data presented partially fulfill the requirements for determining volatility, no attempts were made to identify the volatized compounds and full analytical procedures were not detailed.

Field studies (Stewart and Cairns, 1974, MRID 05003336 and Stanovick, 1966, MRID 00003800) show that endosulfan is degraded to endosulfan sulfate in soil. Residues of endosulfan sulfate and both isomers of endosulfan were present 469-800 days after treatment. Numerous soil monitoring studies (Harris and Sans, 1971, MRID 05002908; Harris et al., 1977, MRID 05005136; Miles and Harris, 1978, MRID 05003003; Mullins et al., 1971, MRID 05003035; Wiersma et al., 1972, MRID 05004938; Carey et al., 1979, MRID 05004976; Carey et al., 1979, MRID 05004978; Frank et al., 1977, MRID 05004013; Frank et al., 1976, MRID 05003049; Miles et al., 1978, MRID 05005044; Harris et al., 1966, MRID 05002907; Carey et al. 1979, MRID 05020171; Wiersma et al., 1972, MRID 05020663; and Carey et al., 1978, MRID 05005978) conducted in North America in the 1960's and 1970's report endosulfan and endosulfan sulfate residues in soil, providing further evidence that endosulfan is persistent in soil. Therefore, annual applications or several applications during a single growing season (which is allowed under the current use patterns) would be expected to result in the accumulation of endosulfan and endosulfan sulfate residues in the soil. The data from these studies are insufficient to determine the dissipation rate of endosulfan.

Numerous aquatic monitoring studies (Frank et al., 1979, MRID 05017234; Frank et al., 1979, MRID 05018066; Frank et al., 1977, MRID 05003337; Glooschenko and Sampson, 1978, MRID 05005248; Greve, 1972, MRID 05004513; Greve and Wit, 1971, MRID 05003342; Herzel, 1972, MRID 05003109; Miles, 1976, MRID 05002902; Miles and Harris, 1971, MRID 05002903; Miles and Harris, 1973, MRID 05003001; Olney, 1972, MRID 05007651; Saleh et al., 1978, MRID 05004418; Gorbach et al., 1971, MRID 05003017 and Wall et al., 1978, MRID 05003366) conducted in North America and Europe report finding endosulfan in water, sediment, and fish samples collected from areas where aquatic crops (watercress) treated with endosulfan are not grown commercially. None of the samples were analyzed for the endosulfan hydrolysis product endosulfan diol.

It cannot be concluded that endosulfan or its degradation products are currently present in the aquatic environment because insufficient data are available.

Data from Ernst (1977, MRID 05003053) indicated a low to moderate endosulfan accumulation potential in the mussel *Mytilus edulis*. At equilibrium, mussels had an endosulfan bioconcentration factor of 600, with soft tissue containing endosulfan at 84 ppb and the water containing endosulfan at 0.14 ppb. A depuration half-life of 34 hours was calculated. However, it must be noted that endosulfan was applied with six other pesticides, and thus interactions among them may have influenced the results.

In experiments conducted by Schimmel (1979, MRID 05005824), bioaccumulation factors of 2755X were found for the whole body of striped mullet, and 2249X for the edible tissue of striped mullet after exposure to 0.08 ppb of endosulfan for 28 days. After 48 hours in endosulfan-free seawater, no insecticide was detected in either the edible or whole body tissues. These two studies collectively satisfy the Guideline requirements for fish accumulation.

In summary, based on the available data, endosulfan will accummulate in the terrestrial environment for several years when applied annually or several times during a single growing season. When applied to soil, endosulfan will be gradually oxidized by microorganisms to endosulfan sulfate. Both endosulfan and endosulfan sulfate are persistent in the environment.

At pH values above 6.5, endosulfan undergoes hydrolysis to endosulfan diol. This process is probably chemical but appears to be accelerated by microbes. Endosulfan diol is degraded to endosulfan alpha-hydroxyether, which is degraded to endosulfan lactone. Endosulfan lactone has been shown to be degraded in aqueous soil culture media, but no data are available on degradation products of endosulfan lactone. In addition, there are no data showing the breakdown of endosulfan's chlorinated ring, which implies that the ring will be stable in the environment. Endosulfan severely inhibits soil microorganisms for approximately 20 days, therefore, repeated applications of endosulfan within this period (which is allowed under the current use patterns) may prolong these inhibitory effects.

In the aquatic environment endosulfan is present in sediment, water, and fish samples. Since it does not appear that these residues are the result of the use of endosulfan in the aquatic environment, endosulfan must be considered as a potential pollutant of the aquatic environment. It is likely that endosulfan diol is also present in the aquatic environment as a result of endosulfan hydrolysis; however, no data are available on the fate of endosulfan diol in the aquatic environment.

C. EXPOSURE PROFILE

The use of airblast machines (which direct the spray upwards) and aircraft sprayers increases the potential for exposure, via spray drift, of humans, livestock, or wildlife outside the application site. Human exposure potential via groundwater contamination cannot be assessed because soil mobility data are lacking. However, the potential for contamination of surface waters was demonstrated by the presence of endosulfan and endosulfan sulfate residues in surface waters sampled in the United States and Canada from 1968-1973. Levels of contamination were generally less than 1 ppb, and the majority of all samples collected did not contain the compounds at detectable levels. Endosulfan residues indicated a potential to accumulate in aquatic organisms. A maximum bioaccumulation factor of 600 was reported in the mussel *Mytilus edulis*, with a depuration half-life of 34 hours. Data were also presented that the bioaccumulation factors in striped mullet ranged from 2249 to 2755X.

The mixers and applicators of endosulfan formulations have the highest potential for direct exposure. Sprayers applying endosulfan with tractor-drawn airblast equipment in Washington State fruit orchards were exposed dermally at an estimated 0.6-95.3 mg/hour (mean 24.7 mg/hour), and respiratory exposure was an estimated 0.02 mg/hour during application (Wolf et al., 1972, MRID 05003239). Another study investigated the duration of pesticide residues on the hands of farmers. Hexane rinsings of the hands of eight farmers revealed endosulfan residue levels from 33.2 down to <0.2 ug, 1-32 days after the last endosulfan application, respectively (Kazen et al., 1974, MRID 05003086).

Although the formulations of endosulfan were not specified in the above studies, the exposures during field applications to fruit trees would be similar for all formulations. Quantitative data are not available to estimate the exposure potential during other kinds of field operations. However, an additional potential for respiratory exposure would occur during opening and mixing of the wettable powder, when "puff back" may contaminate the air. Emulsifiable concentrate formulations increase the potential for dermal exposure during the mixing operations due to splashing of the concentrate.

No data were found to quantify the potential exposure during the use of pressurized liquid or impregnated material formulations on ornamental crops and in greenhouses. Aerial dusting operations may expose flaggers, but again, no data are available to quantify such exposure.

California has set a reentry interval of 48 hours following endosulfan application for all crops.

D. SUMMARY OF DATA GAPS

A number of the guideline requirements have been partially fulfilled by the data submitted. However, data are still needed to adequately assess the environmental fate of endosulfan. The specific deficiencies can be found in the Data Requirement Charts in Chapter III. The data gaps include: hydrolysis, photodegradation, aerobic and anaerobic soil metabolism, leaching, volatility, adsorption/desorption, and terrestrial field dissipation. Data on the following requirements are reserved pending the review and modification of the testing protocols: microbial metabolism, activated sludge metabolism, reentry, and disposal and storage.

VI. TOXICOLOGY

A. Toxicology Profile
B. Human and Domestic Animal Hazard Assessment
C. Summary of Data Gaps

A. TOXICOLOGY PROFILE

No data are available on the acute effects of end-use endosulfan products. Testing will be required to assess the acute oral, dermal, inhalation, and primary eye and dermal irritation effects of representative formulations. The specific data requirements can be found in Chapter III.

1. Acute Effects

Sufficient data are available to show that technical endosulfan has a high acute oral toxicity to mammals and is assigned to Toxicity Category I (see Table 1). Acute intoxication signs are manifested as depression, salivation, lacrimation, labored respiration, tremors and tonic-clonic convulsions. The chemical was also shown to be more toxic to female than to male rats.

There are sufficient data to demonstrate that technical endosulfan is highly toxic to mammals dermally, and can be placed in Toxicity Category I. The seven day dermal LD_{50} values for female rabbits were found to be 167-182 mg/kg for the technical product (Gupta and Chandra, 1975, MRID 05003718).

A combination of two supplementary studies indicated that technical endosulfan is highly toxic to mammals by inhalation. Ely et al. (1967, MRID 05007645) determined that the four hour LC_{50} values for technical endosulfan were 0.35 and 0.08 mg/l for male and female rats, respectively. In another study (Reno, 1975, MRID GS014005), ten male albino rats were exposed to endosulfan technical dust at concentrations of 1.16 and 5.66 mg/l for one hour. The LC_{50} value was not determined. However, it may be estimated to be between 1.16 and 5.66 mg/l. On the basis of the inhalation toxicity data, technical endosulfan is assigned to Category I.

In a study to evaluate the primary eye irritation potential of endosulfan (Reno, 1975, MRID GS014004), six New Zealand rabbits received 83 mg of technical endosulfan in one eye. No corneal opacity was observed but all animals showed slight conjunctivae which cleared in four of the animals by 72 hours. Based on this study, the material can conservatively be assigned to Toxicity Category III for eye irritation.

A primary dermal irritation study was conducted (Reno, 1975, MRID GS014003) in which six New Zealand rabbits were dermally treated with 0.5 gram of endosulfan on abraded and nonabraded skin areas. At 24 hours, all animals exhibited minor erythema; by the end of 72 hours it had cleared in four animals. The primary dermal irritation score was 0.9. This material is therefore assigned to Toxicity Category IV for dermal irritation.

Although endosulfan does not relate to a known group of cholinesterase inhibitors, it was reported by Truhaut et al. (1974, MRID 05011227) to cause the inhibition of hamster serum and rat hepatic cholinesterase. It was also

TABLE 1

Acute Oral LD_{50} Values for Technical Endosulfan

Animal	Sex	LD_{50}	Reference
Sprague Dawley Rats	Male	142 mg/kg	Palazzolo, 1964, MRID 00003762
	Female	53 mg/kg	
Unspecified Rats	Male	110 mg/kg	Elsea, 1957, MRID 00003693
Sherman Rats	Male	43 mg/kg	Gains, 1969, MRID GS014007
	Female	18 mg/kg	
Albino Wistar Rats	Male	102 mg/kg	Boyd et al., 1970, MRID 05002183
Sprague Dawley Rats	Male	40 mg/kg	Reno, 1975, MRID GS014001
	Female	9 mg/kg	
Unspecified Rats	Male	82 mg/kg[1/]	Palazzolo, 1964, MRID 00003762
	Female	21 mg/kg[1/]	
Mice	-	11 mg/kg[2/]	Dorough et al., 1978, MRID 05003703
		36 mg/kg[3/]	
		8 mg/kg[1/]	
		120 mg/kg[4/]	
		270 mg/kg[5/]	
		>2,000 mg/kg[6/]	

1/ The LD_{50} value is for the endosulfan sulfate metabolite.

2/ The LD_{50} value is for the endosulfan I isomer.

3/ The LD_{50} value is for the endosulfan II isomer.

4/ The LD_{50} value is for the -hydroxy ether and lactone metabolites.

5/ The LD_{50} value is for the ether metabolite.

6/ The LD_{50} value is for the diol metabolite.

reported by Gupta (1976, MRID 05007646) that acetylcholinesterase activity in the rat brain was decreased by 23-33 percent after intraperitoneal injection of 30 to 60 mg/kg of endosulfan. Furthermore, the chief signs of acute intoxication were mainly manifested as tremors and clonic convulsions that could be centrally mediated. The intensity of these symptoms correlated well with the concentration of endosulfan in all areas of the central nervous system (Khanna et al., 1979, MRID 05004972). Since the compound causes esterase depression, testing is required to assess the delayed neurotoxic potential of endosulfan. The neurological effects may be included as an additional parameter in the subchronic and/or chronic studies.

2. Subchronic Effects

In a rat subchronic feeding study endosulfan was orally administered to rats daily for 15 days at the rate of 0, 5, or 10 mg/kg. The liver and kidneys appeared to be the organs most affected (Gupta and Chandra, 1977, MRID 05003078). Histopathological examination of the liver and kidney revealed dilation of sinusoid around central veins, areas of focal necrosis and degeneration of hepatocytes and mononuclear monolucocytes, proliferation in the bile duct, and degenerative alterations in the epithelial lining of kidney tubules. Other effects were kupffer cell hyperplasia, inflammatory areas in the subpleural of the lungs and dilation of the alveoli, and severe degeneration of the seminiferous epithelium. A "no observed effect level" (NOEL) could not be established under the conditions of this experiment. This study cannot be used to satisfy the subchronic feeding requirements.

3. Chronic Feeding

In a chronic feeding study (Keller, 1959, MRID 00003602), groups of 50 (25 male and 25 female) Wistar strain rats were fed 0, 10, 30, or 100 ppm of technical endosulfan incorporated in their diets for two years. Gross appearance, behavior, body weight, food consumption, and hematological values were found to be within normal ranges for all groups. A significant decrease in the number of surviving females in the 100 ppm group was reported. Males received 100 ppm showed a slight to moderate growth suppression throughout the study. No increase in the tumor incidence was reported in the treated groups. Significant increase in the absolute and relative weights of kidney were observed in males in the 100 ppm group.

Microscopic examination revealed that the liver and kidneys were the organs most affected by the exposure to the high level of endosulfan. The major kidney lesion manifested as renal tubule dilation, formation of albuminus casts, focal intersititial nephritis, and degeneration of tubule epithilium. Histopathological examination of the livers of males in the 100 ppm group revealed hydrophopic hepatic cells with pale eosinophilic cytoplasmic inclusions.

These liver and kidney changes were not seen in the females that survived the 100 ppm treatment for the duration of the study. The NOEL was considered to be 30 ppm.

However, in addition to the small number of animals that were initially assigned to each test group, the number of animals that survived the two year feeding were also limited. Furthermore, hematological and pathological examinations and the number of animals examined were also limited. In addition, no blood chemistry or urinanalysis were performed. For these reasons, this study was classified as invalid and cannot be used for an adequate assessment of toxic reactions resulting from the chronic ingestion of endosulfan.

In a study by Baran (1967, MRID 00003741) four groups of eight beagle dogs (four males and four females) were administered 0, 3, 10, or 30 ppm of endosulfan in the diet for two years. One male and one female of each group were sacrificed after one year. The rest of the animals were sacrificed at the end of the study. Gross and histopathological examinations were performed on all animals. No abnormal behavioral reactions were noted. Hematological and clinical chemical testing and urinalysis did not reveal significant treatment related effects. Gross and histopathological examinations did not reveal any treatment related effects. The NOEL was considered to be 30 ppm.

Validation of this study was inconclusive. The study had major deficiencies that could render it invalid, e.g. the lack of raw body weight data that prevents complete validation as whether the same animals were used throughout, the presence of differential leukocyte counts record at 18 and 21 months for a male that died at 15 months although these were not included in the final report, histopathological reports were not dated and contained no gross pathology or organ weights, no raw data for food consumption, in addition two females were suspected as being from a previous study. Although providing some information of toxicological value, this study cannot be used to satisfy the chronic feeding requirements.

In another study (Keller, 1959, MRID 00003604) endosulfan was orally administered at the rate of 0.075, 0.25, or 0.75 mg/kg/day in gelatin capsules, six days a week for one year to mongrel dogs. There did not seem to be any treatment related adverse effects with respect to the rate of growth, internal organs weight, biochemical and hematological testing, and urinalysis. Gross and histopathological examinations also did not reveal any significant difference between treated animals and controls. A NOEL is considered to be 0.75 mg/kg or 30 ppm. This study satisfies the Agency requirement for a chronic feeding study in dogs.

4. Oncogenicity

In an oncogenic study in mice, endosulfan was administered in diets at the time weighed average concentrations of 3.5 or 6.9 ppm and 2.0 or 3.9 ppm to males and females respectively (U.S. National Cancer Institute, 1978, MRID 00004256). No treatment related increase in tumors or compound related effects on body weight changes, appearance, or general behavior were observed. However, the high incidence of death among the males precludes the conclusion that endosulfan does not have oncogenic potential and the negative results in this sex should be regarded as inconclusive.

In another study in the same report, endosulfan was administered in the diet to male and female rats at the time weighed average concentrations of 408 and 952 ppm and 223 and 445 ppm respectively. The males in this study showed a significant dose related depression in the rates of growth and survival. The incidence of toxic nephropathy was significantly elevated in both sexes at all dosage levels. A significant increase in parathyroid hyperplasia associated with these renal lesions and testicular atrophy were noted in male rats at both dosage levels. Also associated with the parathyroid lesion was medial calcification of the blood vessels. No evidence of carcinogenicity was found, however, the early death of the male rats preclude the usefulness of any analysis of late developing tumors. As with the mouse study previously discussed, such negative results for the males should be viewed with a great deal of caution. Furthermore, several serious non-neoplastic lesions due to endosulfan treatment were noted at both dose levels. Therefore, it is concluded that any future regulatory actions for endosulfan should await the establishment of no-observable-effect-levels for these lesions.

In another oncogenic study (Bionetics Research Laboratories, 1968, MRID 05010016), endosulfan was tested in two different strains of mice by incorporation in the diet at 3.0 or 6.0 ppm for 18 months or by a single subcutaneous injection. In the feeding study, survival was very poor for both strains at the high dosage level. There were four pulmonary adenomas found in the males at the low dose level against two observed in the controls, and three animals showed hepatomas. A significant increase of pulmonary adenoma in treated mice were also reported with no distinctions between animals of different sex or strain. In the subcutaneous study, there were no significant treatment-related differences in the number of mice surviving for the duration of the experiment. There were no increases in the tumor incidence in the treated groups.

Although providing some information of toxicological value, these oncogenic studies do not meet the current Agency's requirements for oncogenic evaluation, therefore additional studies in both the rat and the mouse are still required.

5. Teratogenicity

A study was conducted by Haley (1972, MRID 00003712) to assess the teratogenic potential of endosulfan. Twenty female Charles River rats were treated orally with 0.5 mg/kg/day, and another 23 females were treated with 1.5 mg/kg/day, from the sixth day through day 15 of gestation. No significant differences were noted between the treated and control animals with respect to mortality and body weight of dams, number of implantations, resorption sites, viable fetuses, fetal skeletal development, and fetal external and internal abnormalities.

Formation of terata was not evident in this study. The higher incidence of changed atria size in the treatment groups perhaps represent a fetotoxic effect. The significance of this finding is dubious, considering the development state of the fetuses and the lack of clear dose response regarding small atria. Hence it must be concluded that further investigation is required to more clearly define the fetotoxic/teratogenic potential of endosulfan.

This study has recently undergone an audit which indicated that the raw data do not support the conclusions in the final report. In addition, the fetuses in all groups were underdeveloped possibly due to the fact that the animals were sacrificed prior to the scheduled 20th day of gestation. There was an unreported increase of the small atria of 59.5 percent in one group and 42.9

percent in the other group. There was also a ten-fold increase in large atria in one group not reported.

As a result of these discrepancies and problems, this study is considered invalid and cannot be used to support the safety of endosulfan with respect to the teratogenic potential.

Gupta et al. (1978, MRID 05003227) investigated the teratogenic and embryotoxic effects of endosulfan in rats. One female rat died in the 5 mg/kg dose group and five females died in the 10 mg/kg group. At the high dose (10 mg/kg), there was a significant increase in the number of litters with resorptions and in litters with skeletal abnormalities. Since no raw data were presented in this study, it cannot be considered a reliable assessment for the teratogenic potential of endosulfan.

In a teratogenic study in the rat, a number of skeletal, visceral, and external anomalies as well as significant reductions in size and weight were reported in fetuses of the high (6 mg/kg) treatment group (Raltech Scientific Service, 1981, MRID GS014008). However, at this dose level, maternal toxicity was evident as manifested by decreased body weight and decreased body weight gain, and clinical observations indicating central nervous system stimulation. The NOEL for fetotoxicity is considered by the authors to be 2 mg/kg.

In another study (Raltech Scientific Services, 1981, MRID GS014023) endosulfan was orally administered to groups of pregnant rabbits at the rate of 0.3, 0.7, or 1.8 mg/kg/day on days 6 to 28 of gestation. Animals were sacrificed on day 29 of gestation. Maternal toxicity was evident in the 1.8 mg/kg group as manifested by noisy and rapid breathing, hyperactivity, convulsions and death. There were no significant differences in the mean number of corbora lutea, implantation efficiency, litter size, sex ratio, mean fetal length and weight or in the number and percent of live and resorbed fetuses.

Gross and histopathological examinations of the fetuses did not reveal any treatment related effects. However, common skeletal variations and anomalies were present in all groups. The NOEL for maternal toxicity is considered to be 0.7 mg/kg/day.

The above studies satisfy the Agency's requirements for teratology data.

6. Mutagenicity

A dominant lethal study in the mouse indicates that the number of implantations, resorptions, and embryos were not affected by endosulfan treatment (Arnold, 1972, MRID 00003711). The results did not indicate a dominant lethal response at 5 and 10 mg/kg.

In another study by Dikshith and Datta (1978, MRID 05003502), endosulfan was administered orally to rats at 0, 11.0, 22.0, 36.0, and 55 mg/kg daily for five days. The rats were injected with 4 mg/kg of colchicine four hours before they were killed by decapitation.

Seminiferous tubules and bone marrows from the femurs were examined. There were no major chromosomal aberrations either in the bone marrow cells or spermatogonial cells. An unspecified number of chromatid breaks with one or two exchange figures were found in the bone marrow cells but not in the spermatogonial cells. There was no chromosomal deletion nor formation of large numbers of fragments. No significant mitotic inhibition were reported in any of the treated groups. No details or quantitative effects data were reported, therefore, no reliable conclusions can be drawn from this study.

In a recent study by Dorough et al. (1978, MRID 05003703), endosulfan and its major metabolites were tested in Salmonella typhimurium mutagenicity test using tester strains TA98, TA100, TA1535, and TA1978. The chemicals were tested at concentrations of 10, 100, 500, and 1000 ug/plate in duplicates in the presence and absence of an activating system. Acetoaminoflourine was included as a positive control. Neither endosulfan I or II, nor any of the metabolites tested showed any increase in the reversion rates beyond the controls, both in the presence or absence of the activating systems. The diol, alpha hyroxy ether, and the lactone metabolites severely inhibited bacterial growth even at the lowest concentration used.

In this experiment it was obvious that only one S-9 concentration and insufficient duplication were used. Furthermore, no raw data were provided. For these reasons this study cannot provide reliable assessment for the mutagenic potenial of endosulfan.

In a supplementary study (Fahrig, 1974, MRID GS014009), endosulfan did not exhibit any positive response when tested for mutagenic potential in Saccharomyces cervisia (mitiotic gene conversion), Escherichia coli (forward mutation), and Serratia marcescens (reverse mutation).

The Agency requires a battery of valid mutagenicity tests which determine the potency of the chemical to induce point mutations and chromosomal mutations either directly or indirectly. The submitted studies do not adequately define the mutagenic potential of endosulfan, and therefore additional testing will be required.

7. Metabolism

The metabolism of endosulfan has been adequately delineated in a number of different mammalian species. In some studies conducted on rats (Dorough et al., 1978, MRID 05003703) it was found that endosulfan metabolites accumulated in tissues, especially in the kidney and liver. Metabolites of endosulfan in the rat include endosulfan sulfate, endosulfan diol, endosulfan ether, endosulfan alpha-hydroxy ether, and endosulfan lactone. The sulfate and alpha-hydroxy ether are the principal metabolites accumulated in tissues. Animals administered endosulfan I eliminated 74.8 percent and 13.2 percent in the feces and urine respectively, while those administered endosulfan II eliminated 68.3 percent and 18.5 percent in the feces and urine respectively in a period of 120 hours. Up to 47 percent of the administered dose was eliminated via the bile. Enterhaptic circulation was not apparent.

In another study (Deema et al., 1966, MRID 00004257) when mice were fed endosulfan, large amounts of endosulfan sulfate were recovered in the liver, small intestine and visceral fat with a trace of this metabolite in the muscle and kidney after 24 hours. Endosulfan was found in the stomach, small intestine and the feces. Endosulfan alcohol was detected in the urine. The principal metabolic products were found to be endosulfan sulfate and alcohol.Schuphan et al. (1968, MRID 05007464) studied the metabolism of radiolabeled endosulfan I and II in rats and mice orally, intraperitoneally and duodenally. The metabolites detected in the feces after the oral and intraperitoneal administration were identified as lactone, alpha-hydroxy ether, and sulfate derivatives of endosulfan in addition to the parent compound. Urine metabolites were identified as the lactone and sulfate derivatives in addition to an unknown metabolite and the parent compounds. Substances detected in the bile after duodenal administration of either isomers were the lactone and the unknown metabolite in addition to traces of the parent compounds. In general, both isomers produced the same type of metabolites, but in different proportions. When both endosulfan I and II were administered in equal amounts, the ratio of the I and II isomers excreted in the urine after 24 hours was 5:1.

Chin and Stanovick (1964, MRID 00003761) found that most of the test material (endosulfan I and II) was excreted in the feces and only traces were detected in the urine of dogs. Endosulfan sulfate was the only metabolite found.

Gupta and Ehrnebo (1979, MRID 05003503) found that after interveneous administration of endosulfan to rabbits, plasma clearance was 2.70+ 1.33 ml/hour/kg for the alpha isomer and 70.1+ 18.6 ml/hour/kg for the beta isomer.

8. Domestic Animal Safety

In a report by Schmidlin and Romann (1971, MRID 05013366), eight cows were accidently fed hay contaminated with 750 to 900 ppm of endosulfan. Three of the animals became severely ill. The symptoms were manifested as tonic-clonic cramps, wobbly gait, dyspnea, muscle twitching, and salivation. One of the three animals had to be sacrificed, the other two recovered after the contaminated feed was removed.

Another case of domestic animal poisoning with endosulfan was reported by Utflev and Westbye (1971, MRID 05012611) when a group of female sheep grazed in a strawberry field that had been sprayed four days earlier with endosulfan. Two of the lambs became ill with initial symptoms of unsteady walk and uncontrolled leg movements, followed by an inability to stand. One animal recovered after 24 hours, while it took one month for the recovery of the second animal. The maximum dose that the animals ingested was estimated to be 5 mg/kg.

Nicholson and Cooper (1977, MRID 05003772) reported accidental poisoning in five calves when they were dusted with 4% endosulfan dust for lice control. About 12 hours later one calf was dead and the remaining four exhibited poisoning symptoms manifested as muscle tremors, twitching of the ears, snapping of the eyelids, violent body jerks, inability to stand, and occasional convulsions. Frenzied activity and aimless jumping were also observed.

In a study conducted by Keller (1959, MRID 00003603) to evaluate the safety of endosulfan to domestic animals, mature lactating Holstein dairy cows were fed radiolabeled endosulfan at levels of 0.0, 0.3, 3.0 and 30 ppm for a period of 30 days. During this period and a subsequent 14 day recovery period, all of the animals exhibited normal appearance and behavior. Food consumption and milk production were within normal limits. At the 3.0 and 30 ppm dietary levels, concentration of labeled endosulfan in the blood gradually increased for the first 21 days, and the level remained essentially the same for the remainder of the period. During the 14-day recovery period there was a 60 and 52 percent reduction in blood endosulfan levels for the 3.0 and 30 ppm doses, respectively. A sharp increase in the amount of labeled endosulfan in milk was observed in the first week. The level remained essentially the same after that and the residue entirely disappeared at the end of the recovery period.

9. Human Toxicity and Epidemiology

Ely et al. (1967, MRID 05007645) reported nine cases of worker exposure to endosulfan dust. All of these cases showed clonic convulsive episodes as the chief symptom of acute intoxication. In all cases the route of exposure was thought to be dermal or inhalational.

Six cases of human exposure to endosulfan were reported by Terziev et al. (1974, MRID 05007645). In all cases, ingestion was the major route of exposure, and five of the six cases were fatal. The signs of acute poisoning were manifested as gagging, vomiting, agitation, tonal writherings, dyspnea, and cyanosis. The deaths occurred within 1.5 to 3 hours. Autopsies in three cases revealed circulatory abnormalities, including edema of the brain and lungs, acute emphysema, and protein dystrophia in the parenchymal organs. Staining showed almost complete chromatolysis at the neurons with karyolysis and vascuolization in some of these cases.

Wolf et al. (1972, MRID 05003239) found that the dermal and respiratory exposure of sprayers to a 0.06% spray of endosulfan was 24.7 mg/hr and 0.02 mg/hr, respectively. The stated exposure equaled 0.27 percent of a toxic dose per hour.

Oudbier et al. (1974, MRID 05001387) measured the exposure to endosulfan using respirator pad analysis and found that exposure was greater during the mixing operation than during spraying. With a five minute exposure time, 182,800 ng were detected on the respirator pad during the mixing while only 4,664 ng were detected during the 30 minute spraying operation.

The potential vulnerability of the central nervous system of humans to endosulfan was demonstrated in epileptic convulsions and altered EEG patterns in three subjects exposed to the pesticide (Tiberia et al., 1970, MRID 00003077). In one of the subjects, occasional EEG alterations were observed a year after the exposure.

10. Pharmacology

Endosulfan was shown to exert a slight contraction action in the rectus muscle of a frog in an experiment using endosulfan at concentrations of 5×10^{-6}M or greater. Acetylcholinesterase effects were observed at 6.5×10^{-5}M (FMC, 1956, MRID GS014006).

In the same study, a lowering of the blood pressure occurred in cats at a dose level of 0.1 mg/kg or higher. At a molar concentration of 3 X 10^{-4}M or higher, endosulfan apparently dampened the frequency and strength of the cat heart beat.

After repeated oral administration of 5 or 10 mg/kg of endosulfan to rats, the compound was detected in the plasma and different parts of the brain (Gupta, 1978, MRID 05003361). The amount of endosulfan I in the brain was in proportion to the blood level of the isomer. This was not the case for endosulfan II whose concentration in the brain was much less than expected from the plasma levels. This indicates the difference in the blood/brain barrier permeability to each of these isomers and may partially explain the difference in their acute toxicities. Other factors that may contribute to the difference in toxicity is the difference in the rate of metabolism and elimination of the two isomers.

Khanna et al. (1979, MRID 05004972) studied the effects of endosulfan on the cat brain. Endosulfan in propylene glycol was administered interveneously at a concentration of 23 mg/kg. The concentration in the lipids of the cat brain 15 minutes and up to six hours after administration was three times greater in the cerebral cortex and cerebellum than in the brain stem and spinal cord. The intensity of the convulsions and tremors correlated well with the concentration of endosulfan in all areas of the central nervous system.

Oral administration of endosulfan to male and female rats at seven or 15 days before an injection of pentobarbital increased liver weights, shortened sleep time, increased induction time and rapidly decreased pentobarbital levels in the blood and brain after 30 minutes (Gupta, 1977, MRID 05003362 and Gupta et al., 1977, MRID 05003363).

Agarwal et al. (1978, MRID 05005443) found that oral administration of endosulfan to rats at 2.5 or 5.0 mg/kg daily for 14 days, induced hepatic lipid peroxidase, aminopyrine-N-demethylase, aniline hydroxylase, and tyrosine aminotransferase.

Endosulfan at 30 and 300 ug/ml did not inhibit liver microsomal-O-demethylase, and at 50 and 500 ug/ml did not inhibit rat or mouse liver UDP-glucuronyl transferase in vitro (Fonberg-Broczek, 1974, MRID 05007036).

11. Emergency Treatment

Supplementary information available (Kretchman, 1971, MRID 00003886) indicates that atropine sulfate was a more effective antidote than pentobarbital, which had only a slight therapeutic effect. Further studies are deemed necessary to elucidate the mode of action of the convulsions and tremors which may be centrally mediated, and to develop a more efficacious antidote for emergency treatment of the acute poisoning cases.

B. HUMAN AND DOMESTIC ANIMAL HAZARD ASSESSMENT

Endosulfan has a very high acute toxicity to mammals via oral, dermal, and inhalational routes. The major symptoms of acute intoxication are manifested as tremors and convulsions indicating the involvement of the central nervous system as a possible target site.

A complete assessment of hazards associated with the long term exposure to endosulfan cannot be made because only one valid chronic study is available. However, there is an indication that the organs most effected by long term exposure are the liver and kidneys. Furthermore, there are indications that the chemical causes parathyroid hyperplasia, testicular atrophy, seminiferous tubular epithelial degeneration, and calcium deposition in blood vessels as a result of chronic exposure. Some of these adverse effects may be attributable to calcium metabolism alteration. Endosulfan did not appear to alter the tumor profiles of female mice and rats, however, no conclusion can be made with respect to the tumorigenesis in males of either species. These aspects will have to be carefully examined in future investigations.

No acute toxicity data have been submitted to evaluate the toxicity of end-use endosulfan products. The endosulfan exposure profile (refer to Chapter V) provides that maximum exposure will occur to those involved in direct mixing, loading, and application of the end-use products. The principal routes of exposure are anticipated to be dermal and inhalational, the latter coming from applicator exposure to spray mist. Until such data are submitted and reviewed, the Agency cannot make an evaluation of the hazards of the various end-use products to humans and domestic animals.

C. SUMMARY OF DATA GAPS

Data gaps for dermal sensitization, acute delayed neurotoxicity, subchronic oral toxicity, subchronic 21 day dermal toxicity, subchronic inhalation toxicity, chronic feeding (rat only), oncogenicity (rat and mouse), reproduction, and mutagenicity must be filled for technical endosulfan. No data were available to assess the acute toxicity (oral, dermal, inhalational, eye and skin irritation) of endosulfan formulations. See Chapter III for the specific requirements for each type of formulation.

VII. RESIDUE CHEMISTRY

A. Residue Chemistry Profile
B. Labeling Requirements
C. Summary of Data Gaps

A. RESIDUE CHEMISTRY PROFILE

1. Uptake, Distribution, and Metabolism in Plants

The absorption, distribution, and metabolic fate of endosulfan have been extensively studied. Endosulfan is not generally translocated in plant tissue. The residue remains where the pesticide application happened to bemade. For example, FMC Corporation (1958, MRID 00003600) compared residues in strawberries by two extraction procedures: macerate extraction of unstripped strawberries versus surface stripping. There was no obvious difference in residue values between the two procedures, leading to the conclusion that endosulfan residues were not absorbed by the strawberries.

In a second study, FMC Corporation (1964, MRID 00003642) showed that total residues of 0.11 to 0.15 ppm in the pulp of sweet potatoes from preplanting soil treatment, while surface residues were from nondetectable to 0.11 ppm. One sample of whole macerated sweet potato showed 0.37 ppm total endosulfan, while other samples had nondetectable residues. In another experiment by FMC (1969, MRID 00003709), there was no detectable residues of endosulfan or endosulfan sulfate in macerate extraction of potatoes, while surface stripping showed low but detectable residues.

Ware et al. (1961, MRID 00003654, and Ware, 1967, MRID 05011420) applied radiolabeled endosulfan to alfalfa. The studies showed a decline in endosulfan residues on the alfalfa, and also showed that endosulfan could be converted to another product whose half-life is greater than endosulfan per se, and shown to be endosulfan sulfate. In addition, traces of the impurity, endosulfan ether, occurred seven days after application.

Harvested alfalfa was treated with endosulfan and subsequently stored under ultraviolet light, sunlight, and dark conditions (Archer, 1973, MRID 05002843). The maximum loss of total endosulfan occurred seven days after application and exposure in the dark, five days on ultraviolet exposure, and six days of sunlight exposure. In all exposure situations endosulfan sulfate as a percentage of total residues increased most dramatically in the dark. Endosulfan I hydroxyether increased in sunlight up to seven days. No endosulfan lactone was detected in any of the exposure situations.

The metabolism of endosulfan in bean plants was studied by Terranova (1962, MRID 05018169) and Terranova and Ware (1963, MRID 05004385). These studies showed that endosulfan I and II, endosulfan alcohol, and endosulfan ether are each absorbed via roots and translocated to aerial plant portions. Foliar application of endosulfan showed some metabolism to endosulfan ether but not to the alcohol metabolite.

Harrison et al. (1967, MRID 05004620) researched the persistence of endosulfan I and II on apple leaves and found the formation of an unidentified material that later was shown to be endosulfan sulfate. Endosulfan sulfate was found to be more persistent than either of the isomers. It composed 75 percent of the total residue on apple leaves at three weeks and 90 percent at eleven weeks.

The metabolism and translocation of endosulfan I and II, endosulfan ether, endosulfan diol, and endosulfan sulfate in bean and sugar beet plants was studied by Beard and Ware (1969, MRID 05002565). Endosulfan sulfate and endosulfan II translocate to roots in both sugar beets and beans, with greater amounts in sugar beet roots. Endosulfan sulfate as a metabolite is translocated, but not when the leaf is treated with endosulfan sulfate _per se_. Endosulfan ether was also found as a plant metabolite.

Chopra and Mahfouz (1977, MRID 05003004 and Chopra and Mahfouz, 1977, MRID 05003801) investigated the metabolism of endosulfan I and II, and endosulfan sulfate in tobacco. The metabolites found were endosulfan sulfate, endosulfan diol (trace), endosulfan ether, and endosulfan lactone. Also endosulfan I was found on endosulfan sulfate treated tobacco but not endosulfan II, indicating the conversion of endosulfan sulfate to endosulfan I. Further, the study found the intraconversion between between endosulfan I and II, and proposed a metabolic pathway for the direct hydrolysis of endosulfan I and II and endosulfan sulfate to endosulfan diol. Another metabolic pathway was endosulfan hydroxyether converting to endosulfan ether and endosulfan lactone.

Stewart and Cairns (1974, MRID 05003336) found that foliar application of endosulfan resulted in endosulfan sulfate in potato peel and pulp at 0.01 ppm, indicating possible translocation of the residue. Absorption of endosulfan I and II and endosulfan sulfate by potato tubers from granular application was much higher than from foliar application. Endosulfan sulfate was found in the pulp while endosulfan I and II and endosulfan sulfate were found in the peel.

The movement of endosulfan into untreated portons of maize plants is reported by Kavadia et al. (1978, MRID 05003085). After foliar application, endosulfan was found in the husks 43 to 63 days later. However, there are no reported results for endosulfan sulfate or other possible endosulfan metabolites.

The metabolism of endosulfan in plants is adequately understood and the residues in plants are endosulfan I and II, and endosulfan sulfate. Endosulfan sulfate is found most frequently on leafy surface crops where there is a large surface to volume ratio. It is less frequently found on root crops such as sugar beets, potatoes, sweet potatoes, or carrots.

2. Metabolism in Food-Producing Animals

The metabolism of endosulfan in animals has been extensively studied in the cow, sheep, swine and chicken.

Stanovick (1965, MRID 00003838) showed that when lactating cows were fed a mixture of endosulfan I and II (5 ppm) plus endosulfan sulfate (5 ppm) in their daily diet for 30 days, no detectable endosulfan I or II was found in the milk, liver, kidney, fat or muscle. Endosulfan sulfate was detected in the milk, fat, liver, kidney, and muscle sampled 30 days after feeding. When the cows were allowed 30 days of feeding without endosulfan, residues in milk declined and residues were found in the fat, but not in the liver, kidney, and muscle.

This indicates some storage in the fat. Since this study did not employ radiolabeled endosulfan, and excreta (other than milk) were not analyzed, a material balance showing the metabolic distribution of endosulfan in the cow cannot be estimated.

Endosulfan and endosulfan sulfate have been reported by Beck et al. (1966, MRID 05003877) in milk and tissues of cattle fed on endosulfan treated silage or grazed in endosulfan treated pastures of Coastal Bermuda grass. Their results showed that although endosulfan sulfate was present in the silage, no detectable residues of endosulfan sulfate were found in the butter fat or omental fat samples. Endosulfan diol was not detected in any silage sample.

In sheep fed commercial grade endosulfan, metabolism and excretion resulted in no endosulfan in the kidney, liver, muscle, brain tissue, kidney fat, or intestinal fat (Gorbach, 1965, MRID 00003743). Up to 20 percent of the administered compound was excreted in the feces. No endosulfan sulfate was found in the feces or urine, but was identified in the milk. In the urine, endosulfan alcohol accounted for 10 percent of the applied endosulfan, and an unidentified endosulfan derivative accounted for another 20 percent.

The metabolism of radiolabeled methylene endosulfan in milk sheep was studied by Gorbach et al. (1966, MRID 05003222). With a material balance of 95 percent, almost half of the radioactivity was excreted in the feces and almost half in the urine. Maximum residues in the tissues were 0.03 mg/g in the liver, less in the large intestine and fat, and less than 0.02 mg/g in other organs and tissues. In the feces, the major component was found to be endosulfan, while the lactone, diol, and hydroxyether metabolites were not detectable (less than 0.5 ppm). In the urine, the two metabolites were endosulfan alcohol and endosulfan I hydroxyether, and two unidentified metabolites. Endosulfan sulfate was the major metabolite in milk (mainly in the cream), but the total amount of compound found in the milk was less than two percent of the applied amount.

The distribution of endosulfan in various tissues of pigs fed technical endosulfan showed endosulfan I and endosulfan sulfate in several bacon samples only (Maier-Bode, 1966, MRID 00003742). No detectable endosulfan I and II, or endosulfan sulfate were found in the liver, gall, spleen, kidney, lungs, heart, brain, spinal cord, pancreas, blood, neck muscle, tongue, or ovary. Endosulfan metabolism is implied by the presence of the sulfate metabolite in the bacon samples.

Chickens fed technical endosulfan at 0.3 and 3.0 ppm in the diet for seven weeks showed no detectable endosulfan I or II, or endosulfan sulfate in the eggs, muscle, heart, liver, gizzards, or intestines (Stanovick, 1967, MRID 00003840). Residues of the I and II isomers were found in the cavity fat at the higher dosage only.

3. Analytical Methods

There are many methods for analysis of endosulfan in a variety of plant and animal tissues. Analytical methods include total chlorine analysis, colorimetric procedures, and gas chromatographic procedures using microcoulometric, electron capture and sulfur detectors.

While original tolerances for endosulfan were based on the two isomers of endosulfan, the residue situation has been complicated by addition of the metabolite endosulfan sulfate to the established tolerances. When endosulfan was first registered, available information was that endosulfan was a mixture of the two isomers, and several manufacturing by-products. In 1963 FMC reported residues of an additional endosulfan related material, which later became known as endosulfan sulfate. The first literature publication dealing with this metabolite was by Cassil and Drummond (1965, MRID 00003795). They found in some instances, up to 70 percent of the endosulfan residue could be endosulfan sulfate. Based on toxicological considerations, it was determined that endosulfan sulfate would be included in the established tolerances. Thereupon, an analytical method for quantitative detection of endosulfan sulfate was required. Since several tolerances for endosulfan had already been established, it was necessary that a certain amount of additional residue data for endosulfan sulfate be required.

A number of residue studies submitted to the Agency were performed prior to the initial finding of endosulfan sulfate, and therefore do not have adequate information regarding the possible presence of endosulfan sulfate. Originally acceptable procedures for total chloride and sulfur dioxide evolution methods have not been shown to be adequate to determine endosulfan sulfate. Microcoulometric gas chromatography had largely supplanted these two methods, and was found to be adequate for the analysis of the sulfate metabolite. However, residue data by the microcoulometric gas chromatography method prior to 1963 are considered adequate for endosulfan per se only, but not adequate for endosulfan sulfate. Only those residue studies which specifically report endosulfan sulfate residues by microcoulemetric gas chromatography procedures are considered adequate to support currently registered uses of endosulfan.

Analytical methods have been submitted for the analysis of endosulfan and endosulfan sulfate residues on plant and animal tissues. Most of the methods are variations on the same basic procedure: endosulfan residues are extracted from the animal or plant tissues by solvents or mixed solvent systems. Extracted residues are further refined by several techniques, including solvent partition or distribution techniques, and adsorption/desorption techniques. When extracted residues are sufficiently purified, gas chromatography is employed for quantitative and qualitative analysis. The nature of the sample dictates the extraction or purification step. Some commodities are high in oil content (cottonseed, rapeseed, nut crops, etc.), while others are low in moisture content. Therefore there is a degree of variability in the exact procedure. The following method descriptions were submitted and deemed adequate for detecting the two endosulfan isomers and endosulfan sulfate on commodities: FMC (19??, MRID 00003959)- carrots, sugar cane, sweet corn, collards, kale, mustard greens, turnip greens, spinach, celery, brussels sprouts, cauliflower, sweet potatoes, peas, snap beans, lima beans, sunflower, and pineapple; FMC (19??, MRID 00003703)- milk and meat; FMC (19??, MRID 00003612)- nut crops; and Stanovick (1967, MRID 00003840)- eggs and poultry tissues.

The Pesticide Analytical Manual, Vol. II, has three methods for the analysis of endosulfan per se. The first method is a microcoulometric gas chromatographic procedure. This method is adequate for enforcement purposes for analysis of both endosulfan and endosulfan sulfate in a variety of nonfatty foods. It is Official First Action for the analysis of endosulfan and endosulfan sulfate in apples and cucumbers. The method is described in Burke and Mills (1963, MRID 05003395).

Method II is a sulfur dioxide evolution method. The sensitivity is estimated at 0.1 to 0.3 ppm of endosulfan per se, and the adequacy for analysis of endosulfan sulfate has not been shown. As far as it is known, only two common pesticides, sulfur and aramite, interfere with this procedure. A procedure for removing sulfur from the spray residue samples has been developed and has been adapted as part of the standard procedure. Differentiation between endosulfan and aramite residues is made by a specific aramite detection method (Gunther et al., 1951, MRID GS014024).

Method III is a microcoulometric gas chromatographic procedure for the analysis of endosulfan in milk and animal tissues. The sensitivity is 0.01 ppm, it is adequate for enforcement purposes, and the method is also adequate for endosulfan sulfate analysis. This method was submitted by FMC with Pesticide Petition No. 8F0632 (FMC, 19??, MRID 00003703).

4. Tolerance Levels

a. Present U.S. Tolerances

According to 40 CFR 180.182 tolerances are established for total residues of endosulfan and its metabolite endosulfan sulfate in or on raw agricultural commodities as follows:

2 parts per million in or on apples, apricots, artichokes, beans, broccoli, brussel sprouts, cabbage, cauliflower, celery, cherries, collards, cucumbers, eggplants, grapes, kale, lettuce, melons, mustard greens, nectarines, peaches, pears, peas (succulent type), peppers, pineapples, plums, prunes, pumpkins, spinach, strawberries, summer squash, sunflower seeds, tomatoes, turnip greens, watercress, and winter squash.

1 part per million in or on alfalfa hay, almond hulls and cottonseed.

0.5 part per million in milk fat (reflecting negligible residues in milk), and in or on sugarcane.

0.3 part per million in or on alfalfa (fresh).

0.2 part per million in or on carrots, sweet corn (kernels plus cob with husks removed), sweet potatoes; and in meat, fat, and meat by-products of cattle, goats, hogs, horses, and sheep.

0.2 part per million (negligible residue) in or on almonds; filberts; macadamia nuts; mustard seed; pecans; potatoes; rape seed; safflower seed; straw of barley, oats, rye, and wheat; and walnuts.

0.1 part per million (negligible residue) in or on blueberries; grain of barley, oats, rye, and wheat; and sugar beets (without tops).

b. International Tolerances

The FAO/WHO Maximum Residue Limit (MRL) for endosulfan are found in Table 2. Like the U.S. tolerances, the FAO/WHO MRLs are for the total combined residues of endosulfan and endosulfan sulfate.

The following commodities (as fruits and vegetables) have the same U.S. tolerances and FAO/WHO MRLs:

apples, apricots, artichokes, beans, blueberries, broccoli, brussels sprouts, cabbage, carrots, cauliflower, celery, cherries, collards, cucumbers, eggplants, grapes, kale, lettuce, melons, mustard greens, nectarines, peaches, pears, peas (succulent type), peppers, pineapples, plums, potatoes, prunes, pumpkins, spinach, strawberries, summer squash, sunflower seed, sweet potatoes, tomatoes, turnips greens, watercress, and winter squash.

TABLE 2

International Tolerances (in ppm)

CROP	FAO/WHO	CANADA	MEXICO	U.S.
Alfalfa (fresh)			0.3	0.3
Alfalfa (hay)			1.0	1.0
Almonds				0.2 nr
Almond (hulls)				1.0
Apples	2.0	2.0	2.0	2.0
Apricots	2.0	2.0		2.0
Artichokes	2.0	1.0	2.0	2.0
Beans	2.0	1.0	2.0	2.0
Blueberries	2.0			0.1 nr
Broccoli	2.0	2.0	2.0	2.0
Brussels sprouts	2.0	2.0		2.0
Cabbage	2.0	2.0		2.0
Carrots	0.2		0.2	0.2
Cauliflower	2.0	1.0		2.0
Celery	2.0	1.0	2.0	2.0
Cherries	2.0	2.0		2.0
Collards	2.0			2.0
Corn (sweet, kernels plus cob with husk removed)	2.0	0.1 nr	0.2	0.2
Cottonseed	1.0*		1.0	1.0
Cucumbers	2.0	1.0	2.0	2.0
Eggplants	2.0	1.0	2.0	2.0
Filberts				0.2 nr
Grapes	2.0	1.0	2.0	2.0
Kale	2.0			2.0
Lettuce	2.0	2.0	2.0	2.0
Macadamia Nuts				0.2 nr
Meat, fat, and meat by-products of cattle, goats, horses and sheep	0.2**	0.1		0.2
Melons	2.0	1.0	2.0	2.0
Milk fat (reflecting negligible residues in milk)	0.5	0.1		0.5
Mustard greens	2.0			2.0
Mustard seed				0.2 nr
Nectarines	2.0			2.0
Peaches	2.0	2.0	2.0	2.0
Pears	2.0	2.0	2.0	2.0
Peas (succulent type)	2.0	0.5	2.0	2.0
Pecans			0.2 nr	0.2 nr
Peppers	2.0	1.0		2.0
Pineapples	2.0		2.0	2.0
Plums (including prunes)	2.0	2.0		2.0
Potatoes	0.2	0.1 nr	0.2 nr	0.2 nr
Pumpkins (including squash)	2.0	1.0		2.0

TABLE 2, continued

CROP	FAO/WHO	CANADA	Mexico	U.S.
Rape seed				0.2 nr
Safflower seed				0.2 nr
Small grains (grains of barley, oats, rye, and wheat)				0.1 nr
Small grains (straw of barley, oats, rye, and wheat)				0.2 nr
Spinach	2.0	2.0	2.0	2.0
Strawberries	2.0	1.0	2.0	2.0
Summer squash	2.0	1.0	2.0	2.0
Sugarbeets (without tops)	2.0	0.1 nr		0.1 nr
Sugarcane			0.02 nr	0.5
Sunflower seeds		0.1 nr		2.0
Sweet potatoes	0.2		0.2	0.2
Tea (dried)	30.0***			24
Tomatoes	2.0	1.0	2.0	2.0
Turnip greens	2.0	0.1 nr		2.0
Walnuts				0.2 nr
Watercress	2.0	1.0		2.0
Winter squash	2.0		2.0	2.0

nr= negligible residues

* FAO/WHO: Cottonseed= 1.0 ppm; Cottonseed oil= 0.5 ppm.

** Carcass Fat

*** Dry, manufactured tea

The Canadian MRLs include endosulfan and endosulfan sulfate.

The negligible residue basis (nr) may or may not include endosulfan sulfate.

Mexican tolerances may or may not include endosulfan sulfate.

5. Residues in Plants and Animals

The reported residue studies for many of the registered uses on raw agricultural products and by-products or feed items are adequate. Several crops or their by-products or feed items are not adequately supported by the residue data. Please refer to the chart in Chapter III for a listing of the citations, which are grouped by the crop listed.

The established tolerances for the following crops are considered adequate and appropriate:

Almonds and Almond hulls
Apricots
Beans
Blueberries
Broccoli
Brussels sprouts
Cabbage
Cauliflower
Collards
Corn (sweet)
Cottonseed
Filberts
Kale
Macadamia nuts
Mustard greens
Mustard seed (oil crop)
Nectarines
Peaches
Peas
Pecans
Plums and Prunes
Potatoes
Rapeseed (oil crop)
Safflower
Small grains (wheat, barley, oats and rye)
Spinach
Strawberries
Sugar beets (without tops)
Sugarcane
Sunflower
Sweet potatoes
Tea
Turnip greens
Walnuts
Watercress

Residue data for total endosulfan in or on the following crops are required:

Alfalfa (seed crop)
Artichokes
Celery
Cherries
Cucumbers
Eggplants
Lettuce
Tomato pomace
Melons, pumpkins, winter squash
Peppers
Squash (summer)
Tomatoes
Apple pomace
Grape and Raisin wastes
Pineapple bran

Residues of endosulfan and endosulfan sulfate in meat and milk resulting from the registered uses are considered Category 1 of 40 CFR 180.6(a) for the following crops or by-products: alfalfa (fresh and hay), almond hulls, small grains (wheat barley, oats, and rye). Category 1 states that finite residues will actually be incurred in meat and milk from feed use of the raw agricultural commodity including its by-products.

Several registered uses on crops which may result in residues in by-products or feed items are considered Category 2 of section 180.6(a). This applies to apples, grapes, tomatoes, pineapple bran, and sugarcane bagasse. Category 2 states that it is not possible to establish with certainty whether finite residues will be incurred, but there is a reasonable expectation of finite residues.

Feeding studies reflecting residues of endosulfan and endosulfan sulfate in poultry and eggs are adequate in showing the possible transfer of residues to poultry and eggs. Residues are not expected in poultry and eggs from registered uses of endosulfan (Category 3 of section 180.6(a)).

6. Dietary Intake

The following reports were reviewed as a series of articles detailing the results of Food and Drug Administration Total Diet Program/Marketbasket Survey. Basic Total Diet samples represent a two week supply of food items, and proportions of a 16 to 19-year old male, a high consumption diet. The food items are prepared for consumption and composited into 12 classes of similar foods. Each class in each sample is a "composite". Analytical methodology is the appropriate multiresidue method, as modified, and all reported residues are confirmed. The size and scope of the program has varied, therefore, one year's results are not directly related to another year. However, the important information is the baseline or frequency of occurrence of pesticide residues in human food items as consumed.

This series of reports by the FDA shows the results of the Total Diet/Marketbasket survey program for the years 1969 to 1975 for composites of similar food crops. During this period, 112 of 2100 composites examined showed trace to measurable amounts of endosulfan and/or endosulfan sulfate.

The highest composite showed 0.44 ppm (FY73) in leafy vegetable composite, but generally the residue levels were less than 0.05 ppm. By crop grouping, endosulfan was found most frequently in leafy vegetables, 59 of 175 composites; garden fruits, 22 of 175 composites; fruits, 18 of 125 composites; potatoes, 12 of 125 composites; and oils, fats and shortening, 1 of 30 composites.

The results of these surveys can be found in Table 3.

7. Residues in Tobacco

The occurrence of endosulfan residues in tobacco and tobacco products has been investigated for a number of years. Although tobacco is not considered a food product, the presence of the pesticide is of interest to account for the total daily intake.

Domanski and Sheets (1973, MRID 05010468) showed the mean level of endosulfan and endosulfan sulfate in auction market tobacco varies by geographic origin (range 0.7 to 3.4 ppm), by tobacco type (range <0.2 to 14 ppm) and by year.

Table 3 RESULTS OF MARKET BASKET SURVEY

CROP GROUPING	PERIOD	FREQUENCY OF RESPONSE	PPM FOUND	REFERENCE
Leafy Vegetables	June 1966 to April 1967	-	<0.001	Duggan and Lipscomb, 1969, MRID 05007360
	June 1969 to April 1970	7 of 30	<0.001 to 0.04	Corneliusson, 1972, MRID 05003701
	June 1970 to April 1971	15 of 30	<0.001 to 0.063	Manske and Corneliusson, 1974, MRID 05005175
	June 1971 to July 1972	7 of 35	<0.001 to 0.028	Manske and Johnson, 1975, MRID 05005255
	August 1972 to July 1973	17 of 30	<0.001 to 0.439	Johnson and Manske, 1976, MRID 05005157
	August 1973 to July 1974	8 of 30	<0.001 to 0.012	Manske and Johnson, 1977, MRID 05005254
	August 1974 to July 1975	5 of 20	<0.001 to 0.022	Johnson and Manske, 1977, MRID 05003080
Garden Fruits	June 1966 to April 1967	-	<0.001	Duggan and Lipscomb, 1969, MRID 05007360
	June 1969 to April 1970	5 of 30	0.001 to 0.005	Corneliusson, 1972, MRID 05003701
	June 1970 to April 1971	2 of 30	<0.001 to 0.061	Manske and Corneliusson, 1974, MRID 05005175
	June 1971 to July 1972	6 of 35	<0.001	Manske and Johnson, 1975, MRID 05005255
	August 1972 to July 1973	4 of 30	<0.001 to 0.002	Johnson and Manske, 1976, MRID 05005157
	August 1973 to July 1974	3 of 30	<0.001 to 0.016	Manske and Johnson, 1977, MRID 05005254
	August 1974 to July 1975	2 of 20	<0.001 to 0.006	Johnson and Manske, 1977, MRID 05003080
Fruits	June 1966 to April 1967	-	<0.001	Duggan and Lipscomb, 1969, MRID 05007360
	June 1969 to April 1970	3 of 30	0.002 to 0.008	Corneliusson, 1972, MRID 05003701
	June 1970 to April 1971	5 of 30	<0.001 to 0.045	Manske and Corneliusson, 1974, MRID 05005175
	June 1971 to July 1972	6 of 35	<0.001 to 0.020	Manske and Johnson, 1975, MRID 05005255
	August 1972 to July 1973	4 of 30	<0.001 to 0.002	Johnson and Manske, 1976, MRID 05005157
Potatoes	June 1966 to April 1967	-	-	Duggan and Lipscomb, 1969, MRID 05007360
	June 1969 to April 1970	3 of 30	0.002 to 0.008	Corneliusson, 1972, MRID 05003701
	June 1970 to April 1971	2 of 30	<0.001 to 0.007	Manske and Corneliusson, 1974, MRID 05005175
	June 1971 to July 1972	1 of 35	<0.001	Manske and Johnson, 1975, MRID 05005255
	August 1973 to July 1974	6 of 30	<0.001 to 0.016	Manske and Johnson, 1977, MRID 05005254
Oils, fats and Shortening	June 1966 to April 1967	-	<0.001	Duggan and Lipscomb, 1969, MRID 05007360
	June 1969 to April 1970	1 of 30	0.185	Corneliusson, 1972, MRID 05003701

Dorough et al. (1973, MRID 05003464) studied the effects of various harvest intervals upon the amount of endosulfan remaining on cured tobacco from top, middle or the bottom of the plant. Increased curing time or increased harvest intervals beyond 14 days did not reduce endosulfan residues. Residues were highest on top leaves but the distribution of endosulfan I and II, and endosulfan sulfate varied in different plant positions.

Keil et al. (1973, MRID 05003122) report that parathion is more persistent through at least the first day, when a mixture of parathion and endosulfan is applied than when parathion alone is applied. This report confirms results in a 1971 study (Keil et al., 1972, MRID 05003032).

Domanski and Guthrie (1974, MRID 05003705) report the average content of total endosulfan in 1972 cigars was 0.41 ppm (range <0.20 to 0.64 ppm) and concluded that these residues were little different than those cigars in 1969 and 1971.

Residues of endosulfan and endosulfan sulfate in various tobacco sold during 1973 are reported below (Domanski et al., 1974, MRID 05003864).

Tobacco Product	Range (ppm)	Mean
Cigarettes	0.36 to 1.27	0.83
Cigars	0.08 to 1.03	0.37
Little cigars	0.15 to 0.26	0.22
Smoking tobacco	0.08 to 0.61	0.37
Chewing tobacco	0.06 to 0.86	0.36
Snuff	0.06 to 0.17	0.12

Gibson et al. (1974, MRID 05003058) reported on chlorinated hydrocarbon pesticides in Kentuckey burley tobacco for 1963 to 1972. Endosulfan residues appeared in one-third of the 1968 auction samples and by 1969 endosulfan became a general contaminant of burley tobacco. Residue levels (0.23 ppm in 1968) rose to over 4.0 ppm in 1972.

Domanski et al. (1975, MRID 05004622) report on the endosulfan and endosulfan sulfate residues in 1972 U.S. auction market tobacco. The mean level in flue-cured tobacco across geographic areas was 0.75 ppm, with a range of 0 to 7.77 ppm. The percentage incidence for residues of endosulfan increased from 22 percent in 1970 to 56 percent in 1972. Burley tobacco in North Carolina was low at 0.06 ppm (mean), and highest in Kentucky at 4.85 ppm (mean). For fire-cured tobacco in Tennessee, the mean residue was 7.34 ppm while in Virginia it was 2.45 ppm. Dark air-cured tobacco in Tennessee was 10.23 ppm (mean) and in Virginia 0.63 ppm (mean). In Maryland, light air-cured tobacco resulted in a mean of 1.34 ppm.

Johnson et al. (1975, MRID 05004164) found that freeze-drying of tobacco shreds resulted in a 43 percent reduction of total endosulfan residues.

Thorstenson and Dorough (1976, MRID 05004164) did not find endosulfan residues in 1969 research grade cigarettes, but 1974 research cigarettes contained endosulfan accounting for 20 to 38 percent of total chlorinated pesticides on these cigarettes. Purchased cigarettes showed endosulfan residue levels of 0.2 ppm (1971), and 0.8 to 1.0 ppm (1972 to 1975).

Frank et al. (1977, MRID 05004013) reported that the mean level of endosulfan residues in cured tobacco leaf in Southern Ontario during 1972-1975 ranged from 2 to 5 ppm, with endosulfan sulfate comprising 40 to 65 percent.

Chopra and Mahfouz (1977, MRID 05003004) reported on the metabolism of endosulfan I and II, and endosulfan sulfate through separate treatments of tobacco leaf. Metabolites found were endosulfan sulfate, endosulfan diol (trace), endosulfan ether, and endosulfan lactone. Endosulfan I was found on endosulfan sulfate treated leaves but not endosulfan II, indicating conversion of endosulfan sulfate to endosulfan I. Furthermore, it was found the intraconversion between endosulfan I and II, and possible metabolic pathway for direct hydrolysis of endosulfan I and II and endosulfan sulfate to endosulfan diol. A possible reaction converting endosulfan hydroxyether to endosulfan ether and endosulfan lactone is proposed. Additionally, endosulfan I was the metabolite of endosulfan sulfate on green tobacco leaves, while endosulfan II was the main metabolite of endosulfan sulfate on cured tobacco leaves.

Chopra et al. (1978, MRID 05003138) investigated the pyrolytic degradation of endosulfan I. The pyrolysis products were endosulfan I and II, endosulfan ether, hexachlorocyclopentadiene, chlorobenzenes, methyl chloride, dichloromethane, chloroform, carbon tetrachloride, 1,1-dichloroethylene, 1,1-dichloroethane, trichloroethylene, and tetrachloroethylene. From these reaction products in a nitrogen atmosphere, the following endosulfan degradation products may occur in tobacco and cigarette smoke: endosulfan I and II, endosulfan sulfate, endosulfan ether, endosulfan lactone, mono-, di-, tri-, and tetrachlorobenzenes, and hexachlorocyclopentadiene.

B. LABELING REQUIREMENTS

Labeling of endosulfan products should bear a warning or restriction against use, storage, or disposal of endosulfan formulations in a manner likely to result in contamination of human food items.

Each use of registered endosulfan products must bear appropriate use directions, warnings, limitations, or restrictions. For food crops, the restrictions include such aspects as the maximum permitted dose, the timing and frequency of application, duration of any preharvest interval, and grazing, foraging, or feeding restrictions to prevent the transfer of residues to animals. These restrictions, limitations or label instructions are based upon adequate residue data.

The current labeling of end-use products should be retained in the present format for all crops and formulations with the following exceptions:

Nut Crops:

Almonds, Filberts, Macadamia Nuts, Pecans, Walnuts.

"Do not graze livestock on orchard crops or grasses in treated areas."

Tree Fruit Crops:

Apples, apricots, cherries, nectarines, peaches, pears, plums and prunes.

"Do not feed cull fruits to animals nor allow livestock to graze treated orchards."

Corn (Field, grown for seed)

"Do not feed forage or ensilage to livestock or allow livestock to graze in treated fields."

"Do not make more than five applications."

Eggplants

Dusts:

"Do not exceed 1.0 pounds active ingredient endosulfan per acre."

Emulsifiable Concentrates or Wettable Powders:

"Do not exceed 0.5 pounds active ingredient endosulfan per acre"

Pumpkins

Emulsifiable Concentrate:

"Do not apply within one day of harvest."

Peas (seed crops)

"Do not apply more than two times during the fruiting season. Do not feed treated vines to livestock or allow livestock to graze in treated fields. Use only on peas to be harvested by combine.

Turnip Greens

"Do not apply to turnips grown for roots."

C. SUMMARY OF DATA GAPS

Data will need to be submitted on the residues of endosulfan and endosulfan sulfate on a number of crops and animal foodstuffs. The specific crops are listed in the Data Requirement Charts in Chapter III.

VIII. ECOLOGICAL EFFECTS

A. Ecological Effects Profile
B. Ecological Effects Hazard Assessment
C. Summary of Data Gaps

ECOLOGICAL EFFECTS PROFILE

Endosulfan, as noted earlier in the Use Summary section in Chapter V, is an insecticide applied to agricultural and commercial ornamental crops. It may be applied by ground or aerial equipment to these crops and as a result of these methods of application, some potential exists for the exposure of nontarget terrestrial and aquatic organisms. A scientifically sound data base on the toxicity of technical and end-use endosulfan to nontarget organisms is not complete, and additional testing and monitoring will be required as noted in the Data Requirement Charts in Chapter III.

1. Avian Studies

A mallard duck oral LD_{50} study was performed with technical endosulfan and the LD_{50} value was found to be 34.4 mg/kg (Hudson et al., 1972, MRID 05003462). A study conducted on starlings found the LD_{50} value to be 35 mg/kg (Schafer, 1972, MRID GS014015). Technical endosulfan can therefore be considered to be highly toxic to avian species.

One dietary study tested several species using technical endosulfan (Hill et al. 1975, MRID 00022923) and resulted in the following LC_{50} values: young Bobwhite quail- 805 ppm; Japanese quail- 1250 ppm; Ring-necked pheasant- 1275 ppm; and mallard duck- 1053 ppm. Technical endosulfan can therefore be considered slightly to moderately toxic to upland game birds and waterfowl when administered in subacute dietary tests.

2. Aquatic Organism Studies

A 48 hour LC_{50} study using technical endosulfan was performed on the water flea (Daphnia magna), resulting in an LC_{50} value of 166 ppb (Macek et al., 1976, MRID 05008271). Two studies tested technical endosulfan with scuds and obtained the following results: 48-hour LC_{50} for Gammarus lacustris is 9.2 ppb (Sanders, 1969, MRID 05009242) and the 96-hour LC_{50} for Gammarus fasciatus is 6 ppb (Sanders, 1972, MRID 05017538). Technical endosulfan is considered to be very highly toxic to freshwater invertebrates.

Utilizing an 86% technical sample of endosulfan, the 96-hour LC_{50} value for rainbow trout was determined to be 0.37 ppb (EPA, 1976, MRID GS014012). The 96-hour LC_{50} for an unspecified percentage of technical endosulfan was found to be 1.5 ppb for rainbow trout (Macek, 1969, MRID 05003107).

One acute 96-hour LC_{50} study (EPA, 1976, MRID GS014011) tested the 50% wettable powder formulation on rainbow trout, and found the LC_{50} value to be 0.47 ppb. A 4% dust formulation was tested on rainbow trout by Ludeman (1972, MRID GS014010) and the 96-hour LC_{50} value is 28 ppb. These acute toxicity data indicate that technical, wettable powder, and dust formulations of endosulfan are very highly toxic to coldwater fish. Results from three 96 hour LC_{50} studies on bluegill sunfish are reported in Table 4.

Table 4

Toxicity of Technical Endosulfan to Bluegill Sunfish

Composition	LC_{50}	Reference
100% Technical Endosulfan	1.7 ppb	Buccafusco and Sleight, 1976, MRID GS014014
86% Technical Endosulfan	2.08 ppb	EPA, 1976, MRID GS014012
96% Technical Endosulfan	3.3 ppb (soft water)	Pickering and Henderson, 1966, MRID 05014941
96% Technical Endosulfan	4.4 ppb (hard water)	Pickering and Henderson, 1966, MRID 05014941

These LC_{50} values demonstrate that technical endosulfan is very highly toxic to warmwater fish, regardless of water hardness.

Two additional studies were available on the acute toxicity of technical endosulfan to warmwater fish. In the first, Pickering and Henderson (1966, MRID 05014941) found the LC_{50} value for an unspecified guppy to be 3.7 ppb in soft water, and Macek et al. (1976, MRID 05008271) found the LC_{50} for the fathead minnow to be 0.86 ppb. These results help to confirm the very high toxicity of technical endosulfan to warmwater fish.

A few studies were conducted on exotic fish. The multiplicity of similar values provides for confidence in extrapolating the results to native North American fish. Amminikutty et al. (1977, MRID 05003103) found the 96 hour LC_{50} value for the widow tetra (Gymnocorymbus tertnatzi) to be 1.6 ppb, using a 35% emulsifiable concentrate formulation. Basak and Konar (1976, MRID 05004792) found the following 96 hour LC_{50} values using the 35% emulsifiable concentrate formulation: Tilapia mossambicus - 1.4 ppb; Cyprinus carpio (common carp)- 0.9 ppb; and Heteropenustes fossilis - 1.5 ppb. The above values reveal that the 35% emulsifiable concentrate formulation is very highly toxic to these fish.

Three acute toxicity tests were conducted using technical endosulfan with marine/estuarine fish and are reported in Table 5.

Schimmel (1979, MRID 05005824) also studied the acute effects of technical endosulfan on estuarine invertebrates. The 96 hour LC_{50} values for the 100% technical material were 0.04 ppb for pink shrimp and 1.3 ppb for grass shrimp. Technical endosulfan is considered to be very highly toxic to estuarine invertebrates.

The Schimmel study also examined the bioaccumulation potential of endosulfan in striped mullet, an estuarine fish. Using 100% technical endosulfan at a concentration in the water of 0.8 ppb, after 28 days the concentration factor was 2249 in edible tissue and 2755 in the whole body. No detectable residues could be found after 48 hours depuration.

In a study by Roberts (1975, MRID 05003062), mussels and scallops were exposed to 450 ppb technical endosulfan for 24 hours. Observations showed a 50 percent reduction in byssal attachment, probably resulting from a reduction in pedal activity or blockage of synthesis of byssal components.

4. Amphibian Studies

There is sufficient information to characterize the field toxicity of endosulfan to amphibians as highly toxic. In using an unknown formulation, Mulla (1962, MRID 05020175) found that 0.1-0.5 pounds of active ingredient per acre was "toxic" to bullfrogs. No details were elucidated as to the toxic effects. In another experiment, Mulla (1963, MRID 05011390) found moderate mortality to tadpoles at 0.1 pound active ingredient per acre (endosulfan II) and complete kill at 0.5 pounds per acre (endosulfan I).

Table 5

Acute Toxicity of Technical Endosulfan to Marine/Estuarine Fish

Composition	Species	LC_{50}	Reference
96% Technical Endosulfan	Striped Bass	0.2 ppb	Earnest, 1970, MRID 00001328
Unspecified Technical	Striped Bass	1000 ppb	Korn et al., 1974, MRID 05000819
100% Technical Endosulfan	Pinfish	0.3 ppb	Schimmel, 1979, MRID 05005824
100% Technical Endosulfan	Spot	0.09 ppb	Schimmel, 1979, MRID 05005824
100% Technical Endosulfan	Striped Mullet	0.38 ppb	Schimmel, 1979, MRID 05005824

All the values indicate that technical endosulfan is very highly toxic to marine/estuarine fish.

5. Nontarget Soil and Surface Invertebrate Studies

In studies with various species of parasitic wasps, endosulfan was found to be low in toxicity (Davies and McLaren, 1977, MRID 05004003 and Bartlett, 1966, MRID 05005640) and as moderately to highly toxic (Bartlett, 1963, MRID 05003978 and Searle, 1965, MRID 05005572). One study indicated that endosulfan was not sufficiently selective against a pest species to be useful in integrated control (Coutin and Coulon, 1966, MRID 05005993). The addition of oil was found to significantly reduce toxicity of endosulfan to one species of parasitic wasp (Searle, 1964, MRID 05006416). The available information indicates that endosulfan toxicity to parasitic wasps is highly variable, depending on formulation, route of exposure, and test species.

A similar situation exists with regard to endosulfan toxicity to predaceous beetles. Studies indicate low toxicity (Bartlett, 1966, MRID 05005640 and Teotia and Tiwari, 1972, MRID 05013372), high toxicity (Bartlett, 1963, MRID 05003978), or a toxicity range from low to high, depending on formulation, life stage of insect, etc. (Kundu and Sharma, 1974, MRID 05004542; Colburn and Asquith, 1971, MRID 05004007; and Bartlett, 1966, MRID 05005640). Data from two studies (Croft and Nelson, 1972, MRID 05009345 and Bartlett, 1964, MRID 05004148) indicate that endosulfan is moderately to highly toxic to predaceous mites in the genus *Amblyseius*.

6. Beneficial Insect Studies

Endosulfan was shown to be low in toxicity to honey bees in two laboratory studies (Clinch, 1967, MRID 05008936 and Johansen, 1972, MRID 05000837), and moderately toxic in six studies (Atkins and Anderson, 1967, MRID 00001999; Stevenson, 1978, MRID 05001991; Harris and Svec, 1969, MRID 05011163; Palmer-Jones, 1958, MRID 05004413; Okada and Hoshiba, 1970, MRID 05013090; and Stevenson, 1968, MRID 05004151). Several field studies reported no adverse effects on exposed colonies of honey bees (Palmer-Jones and Forster, 1963, MRID 05004412; Palmer-Jones, 1959, MRID 05004414; Palmer-Jones et al., 1959, MRID 05004794; and Gorecki, 1973, MRID 05012881).

With regard to other pollinators, endosulfan tests proved to be relatively nontoxic to Indian honey bees (Singh et al., 1974, MRID 05003360 and Attri and Sharma, 1969, MRID 05004597), highly toxic to alkali bees (Johansen, 1972, MRID 05000837), and moderately to highly toxic to the alfalfa leafcutter bee (Johansen, 1972, MRID 05000837 and Tasei et al., 1977, MRID 05013358).

B. ECOLOGICAL EFFECTS HAZARD ASSESSMENT

1. Introduction

Endosulfan products are registered for a wide variety of sites, including large and small acreage commercial field and food crops, fruit trees, nuts, and ornamental trees, shrubs, and plants. Several greenhouse uses are also registered.

The outdoor uses are of particular concern for fish and wildlife safety. Applications to watercress, a relatively minor commercial crop, is however, the most hazardous use for aquatic organisms since this requires a direct application to water. There are documented reports of fish kills resulting from uses on tomatoes, lettuce and cropdusting. These reports can be found in the Agency's files.

The mechanisms of mobility providing for contamination of aquatic sites following applications of endosulfan to terrestrial crops may include runoff, soil erosion (with bound residues), and drift. Drift may provide for contamination of nonterrestrial sites, while direct contamination of aquatic sites results from the watercress use. Leaching has not been addressed in the submitted studies, therefore the attendant hazard potential is not assessable at this time.

While the submitted studies are not sufficient to fully assess the environmental fate and mobility of endosulfan at this time (see Chapter V), a consideration of several of its known physico-chemical characteristics is essential to this initial hazard assessment.

2. Aquatic Hazard Assessment

Freshwater invertebrate tests indicate that sensitivity to endosulfan greatly increases with time of exposure and that toxicity may be species specific. The lethal levels are taken to be 6-10 ppb in acute exposure situations. Acute mortalities are expected even in cases of very low aquatic contamination, and certainly in aquatic use patterns.

Considering known toxicological data, significant acute adverse effects are expected for all freshwater and marine/estuarine fish and invertebrates exposed to aquatic residues (at levels 0.5 ppb) of endosulfan and its metabolites. Some species may be severely affected at 0.25 ppb. Acute effects include mortality at greater than or equal to 50 percent of exposed populations. Bioaccumulation and histopathological subacute adverse effects have been demonstrated in aquatic organisms including fish, and are likely to occur at low ambient levels. The likelihood of adverse reproductive effects on fish or aquatic invertebrates is not assessable at this time due to data gaps, although some effects on aquatic invertebrate spawning has been demonstrated.

Fish and aquatic invertebrate kill reports (MRID GS014016) suggest that levels of endosulfan resulting in acute mortality are observed after label recommended use on some field crops. Use on watercress is almost certain to result in residues far exceeding LC_{50} values for all aquatic species tested. Aquatic residues at the application site greater than one-half the LC_{50} are clearly exceeded in the watercress use pattern, where Agency calculations show 734 ppb as the expected aquatic residue in a one-half acre-foot of water (367 ppb in one acre-foot, 61 ppb in 6 acre-feet, 37 ppb in 10 acre-feet). However, the likelihood of acute effects resulting from mobility of endosulfan residues from the watercress use pattern is not assessable at this time because of toxicity and field monitoring data gaps. Accordingly, the results from field monitoring studies required by the environmental fate chapter will be needed to fully assess the aquatic hazards resulting from direct applications to water and those due to runoff, soil erosion and drift into freshwaters and estuaries.

Many of the crops covered by existing registrations are grown near or adjacent to estuaries containing valuable fisheries resources. These resources are thus exposed to contamination via runoff, soil erosion and drift. These are particularly important as habitats for breeding and brood rearing of many estuarine and marine species. The required field monitoring must, therefore, include estuarine habitats exposed by adjacent crop treatments. It should be noted that adverse effects to estuarine species could be more pronounced due to the variance of water flux in certain estuaries. This could result in exposures resembling static conditions. Some estuarine species (spot, mullet, pinfish, and shrimp) are affected at extremely low levels of endosulfan (LC_{50} value for spot is 0.04 ppb). The Agency has fish kill reports of instances when endosulfan has been measured in various aquatic components, especially after aerial spraying of tomatoes. Ambient levels in affected estuaries were measured as low as 0.14 ppb after these fish kills (MRID GS014016).

The hazard to amphibians is poorly understood at this time. The Agency has reviewed only two inconclusive field studies which showed "highly toxic" effects. The Agency considers these hazards to be equal to or more severe thanthose for fish, since the amphibian aquatic larvae may be more susceptible to pesticidal effects. The larval amphibian hazards may be even more pronounced than those for fish, as these larvae are frequently found in shallow depths, such as pond edges, drainage/irrigation ditches and canals, temporary ponds, flooded fields, swamps, bogs, shallow streams, and marshes. The amphibian hazard assessment must await results from the field monitoring, as required in the environmental fate chapter.

3. Terrestrial Hazard Assessment

Hazards to terrestrial species cannot be fully assessed because of the data gaps, particularly in reproduction tests. Since aquatic monitoring is required (see above) a crop by crop analysis will not be presented, but rather the Agency will address residues and routes of intoxication in this standard.

Effects (or lack thereof) on avian and mammalian reproduction have not been addressed in the submitted studies. This information is required to be submitted. Dietary residues may result in adverse effects on avian reproduction.

Avian and mammalian dietary toxicity via the drinking water route has not been specifically addressed, but it is assumed to be at least as toxic as the feed route, and may be more so due to the ease of absorption into the blood after drinking. Volatilization, likewise, has not been specifically addressed in the submitted studies and these data are required. Drift from applications of dust and emulsifiable concentrate formulations could present an acute problem for terrestrial species via inhalational and dermal exposure.

C. SUMMARY OF DATA GAPS

Data must be submitted to satisfy the following data requirements: avian single dose oral LD_{50}, avian reproduction, data on the acute LC_{50} for a coldwater fish, acute toxicity to crabs and mollusks, and testing of all endosulfan formulations on the acute toxicity to aquatic invertebrates and to estuarine and marine organisms.

IX. CASE BIBLIOGRAPHY

Guide to Use of This Bibliography

1. Content of Bibliography. This bibliography contains citations of all the studies reviewed by EPA in arriving at the positions and conclusions stated elsewhere in the standard. The bibliography is divided into two sections: (1) citations that contributed information useful to the review of the chemical and considered to be part of the data base supporting registrations under the standard, and (2) citations examined and judged to be inappropriate for use in developing the standard. This second part of the bibliography exists in the Agency's files and does not accompany this standard. Interested parties may request a copy from the Agency. Primary sources for studies in this bibliography have been the body of data submitted to EPA and its predecessor agencies in support of past regulatory decisions, and the published technical literature.

2. Units of Entry. The unit of entry in this bibliography is called a "study". In the case of published materials, this corresponde closely to an article. In the case of unpublished materials submitted to the Agency, the Agency has sought to identify documents at a level parallel to the published article from within the typically larger volumes in which they were submitted. The resulting "studies" generally have a distinct title (or at least a single subject), can stand alone for purposes of review, and can be described with a conventional bibliographic citation. The Agency has attempted also to unite basic documents and commentaries upon them, treating them as a single study.

3. Identification of Entries. The entries in this bibliography are sorted by author, date of the document, and title. Each entry bears, to the left of the citation proper, an eight-digit numeric identifier. This number is unique to the citatiuons, and should be used at any time specific reference is required. This number is called the "Master Record Identifier", or "MRID". It is not related to the six-digit "Accession Number" which has been used to identify volumes of submitted data; see paragraph 4(d)(4) below for a further explanation. In a few cases, entries added to the bibliography late in the review may be preceded by an eight-character temporary identifier. This is also to be used whenever specific reference is needed.

4. Form of the Entry. In addition to the Master Record Identifier (MRID), each entry consists of a bibliographic citation containing standard elements followed, in the case of materials submitted to EPA, by a description of the earliest known submission. The bibliographic conventions used reflect the standards of the American National Standards Institute (ANSI), expanded to provide for certain special needs. Some explanatory notes of specific elements follow:

    a. Author. Whenever the Agency could confidently identify one, the Agency has chosen to show a personal author. When no individual was identified, the Agency has shown an identifiable laboratory or testing facility as author. As a last resort, the Agency has shown the first known submitter as author.

b. Document Date. When the data appears as four digits with no question marks, the Agency took it directly from the document. When a four-digit date is followed by a question mark, the bibliographer deduced the date from evidence in the document. When the date appears as (19??), the Agency was unable to determine or estimate the date of the document.

c. Title. This is the third element in the citation. In some cases it has been necessary for Agency bibliographers to create or enhance a document title. Any such editorial insertions are contained between square brackets.

d. Trailing Parentheses. For studies submitted to the Agency in the past, the trailing parentheses include (in addition to any self-explanatory text) the following elements describing the earliest known submission:

    (1) Submission Date. Immediately following the word 'received' appears the date of the earliest known submission.

    (2) Administrative Number. The next element, immediately following the word 'under', is the registration number, experimental permit number, petition number, or other administrative number associated with the earliest known submission.

    (3) Submitter. The third element is the submitter, following the phrase 'submitted by'. When authorship is defaulted to the submitter, this element is omitted.

    (4) Volume Identification. The final element in the trailing parenthesis identifies the EPA accession number of the volume in which the original submission of the study appears. The six-digit accession number follows the symbol 'CDL', standing for "Company Data Library". This accession number is in turn followed by an alphabetic suffix which shows the relative position of the study within the volume. For example, within accession number 123456, the first study would be 123456-A; the second, 123456-B; the 26th, 123456-Z; and the 27th, 123456-AA.

OFFICE OF PESTICIDE PROGRAMS
REGISTRATION STANDARD BIBLIOGRAPHY
Citations Considered to be Part of the Data Base Supporting
Registrations Under the Standard

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